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Hypopituitarism Associated with Epilepsy Following Head Injury

Report of Two Cases[1]

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IN THE course of our studies on hypopituitarism we have found that the pattern varies considerably from case to case. In women the usual picture is that described by Sheehan (1). In men there are a variety of causes for the condition. Among others, we have found two in whom it developed following head injuries. The association of the manifestations of hypopituitarism with epileptiform seizures in these two cases seems to us of sufficient interest to warrant publication. We have made rather extensive clinical and laboratory studies on both cases and have an autopsy on one.

[1] Read before the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 12, 1944.

CASE REPORTS

The case reports are as follows: the first patient, *J. S. (unit no. 396,128)*, a 46 year old married Jewish factory worker, was referred to one of us (J. L.), because of a "gland condition" and convulsions. For many years—20 or more—he had suffered every 4–6 weeks with attacks, which were epileptiform in character. The attacks were not accompanied by visual, auditory or uncinate aura. The frequency of the attacks was only partially controlled by phenobarbital which he had been taking for 15 years. There was no family history of epilepsy.

The patient had always been rather short, was slow mentally and physically, perspired

very little, had a poor memory and dozed off rather easily. He had been told several years previously that he had a low blood pressure. He shaved infrequently, had very little axillary, pubic or body hair and had never had an erection or ejaculation despite 14 years of married life.

At the age of 15 he was shot accidentally, the bullet entering the left orbit, and was unconscious for several days. At an Emergency Hospital where he was taken, the surgeon probed for the bullet but apparently did not find it. He did not know whether x-ray studies were made or not. The patient opined that all his difficulties began soon after this accident.

Examination showed a short, slow-moving male with characteristic hypopituitary features (see fig. 1*). His weight was 55 kg., height 151.5 cm., and span 140.5 cm. He was described as "baby faced," with eunuchoid configuration—narrow shoulders and broad hips—and feminine hands. His skin was cold, soft and thin. He lacked axillary and body hair but had a little pubic hair which was "female" in distribution. The hair on his scalp was abundant and coarse. There was a scar at the medial corner of the left upper lid, presumably where the bullet struck. The left

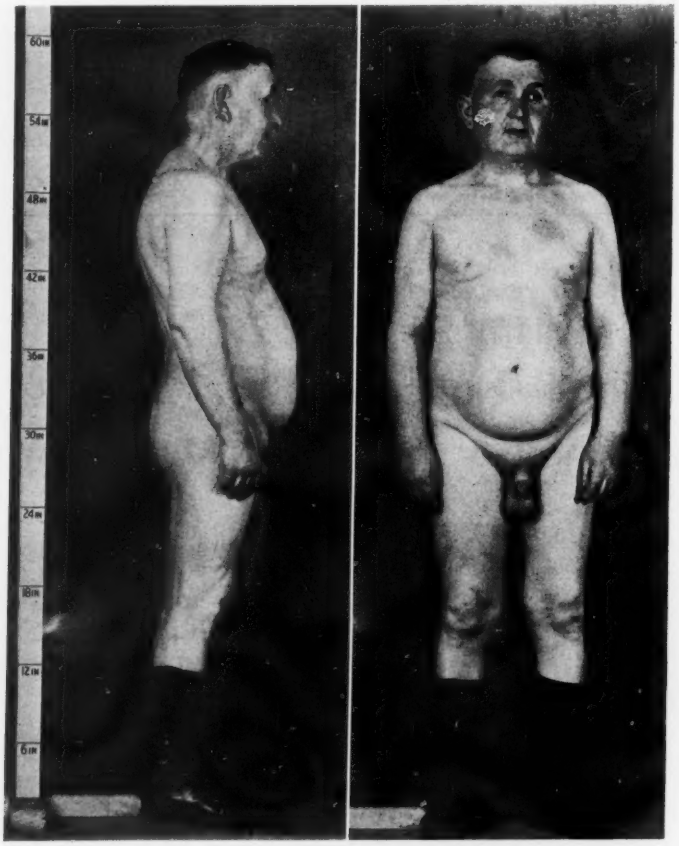

FIG. 1. Photograph of *Case 1 (J.S.)*. Although this picture was taken sometime after the beginning of treatment, it still illustrates his hypopituitary features.

* This photograph was obtained after treatment was underway. Unfortunately we were unable to secure one before treatment because of a shortage of facilities.

pupil was irregular and larger than the right. Vision on the left was impaired by a traumatic cataract. The visual fields by rough tests, later confirmed by perimeter tests, showed left homonomous hemianopsia. The heart was normal, with pulse of 54 and blood pressure of 96/68. The penis was rather small, the testes were soft and about half the normal size, and the prostate was also about half the expected size. He had a normal urine and blood picture.

The diagnosis of hypopituitarism complicated by epilepsy was clear and the mechanism by which trauma had produced this syndrome was predicted at the first examination, and later verified by skull skiagrams (see fig. 2a, 2b). There was an irregular bullet fragment, 1 cm. in diameter, just behind and slightly lateral to the right posterior clinoid, with a smaller fragment lying above, anteriorly and medially. Numerous tiny metallic fragments were scattered from the region of the pituitary fossa to the left orbit, outlining the path traversed by the bullet. There was a small defect in the bony roof of the left orbit, probably representing the entry of the bullet. The epiphyses of all the extremities were closed. The heart and lungs were normal by x-ray examination.

Some of the pertinent laboratory data were normal: the fasting blood sugar was 79 mg. per cent; the non-protein nitrogen, 20 mg. per cent; the serum protein, 7.3 gm. per cent; the blood cholesterol, 195 mg. per cent; and the excretion of lead was normal. Many of the data, however, confirmed the diagnosis. The blood sodium was 138 m.eq. per liter; the blood chloride, 96 m.eq. per liter—both slightly low values—and the water excretion test was consistent with a state of hypocorticism. The insulin tolerance test, as indicated in figure 3, was characteristic of hypopituitarism by dropping rapidly to a low blood sugar level, but was normal otherwise in that the blood sugar returned to the fasting level in 2 hours. The basal metabolic rate fluctuated, but usually hovered between minus 30 and minus 40, and the protein-bound iodine was 3.8 gamma per cent. The excretion of 17-ketosteroids in the urine was 3.2 mg. per 24 hours—a very low value for a male; biopsy of the testicle showed marked hypospermiogenesis and absence of Leydig cells. The excretion of FSH in the urine was in the low normal range. Visual fields showed left homonymous hemianopsia with splitting of the macula; the electroencephalogram, as shown in figure 4, was grossly and diffusely abnormal. The frequency of the rhythm was 7 to 7.5 per second, which is slower than normal but consistent with the general depression of metabolism. There was more abnormality in the right occipital region during quiet breathing and in the left temporo-parietal, during overbreathing. In general the record showed lateralization to the left, in spite of the fact that the bullet fragments were lodged to the right of the midline.

It was obvious from the x-ray and other findings that the bullet had destroyed the major part, if not all, of the anterior lobe of the pituitary and perhaps the posterior lobe as well. The fragments must have injured the right optic tract or the right posterior cerebral artery, and were, in all probability, the cause of the epileptiform seizures. Dr. J. C. White, our neurosurgeon, indicated that one of the fragments was lodged in the interpeduncular system, touching the lateral edge of the right peduncle and the mesial portion of the right temporal lobe, and another in the right optic tract or the lenticular nucleus.

Since it seemed that surgical removal of the bullet fragments was impracticable, treatment was directed mainly to the endocrine abnormality. Several types of gonadotropins were tested and results will be reported in another paper.

At present he is taking 30 mg. of desiccated thyroid daily, and 4 grams of salt to protect him against adrenal failure. He feels considerably better than when first seen. His metabolism ranges about minus 20, but he continues to have epileptic seizures of varying severity. Recently a series of injections of testosterone produced some improvement in endocrine status, also without affecting the convulsive seizures.

The second patient, *C. H. (unit no. 85832)*, 48 years old, a male watchman, first came un-

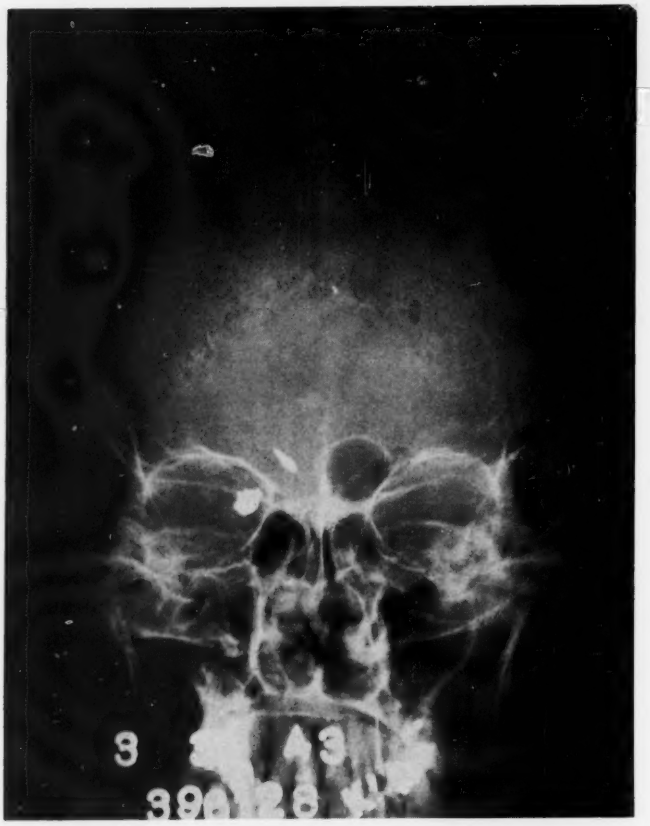

FIG. 2 a.

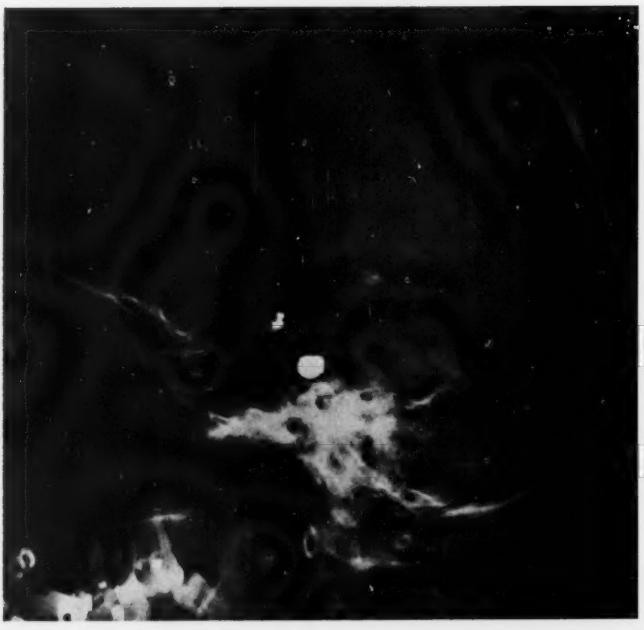

FIG. 2 b.

der our observation in October, 1943. During the first World War, while serving with the English Army in France, he had an attack of rheumatic fever. Later, in 1917, he was injured on the battlefield by the explosion of a shell. He was buried under debris and was nervous system disease, considered to be due either to syphilis or to tuberculosis. At this time a slight anemia of 3.5 million erythrocytes was present. Central nervous system syphilis was the accepted diagnosis in spite of a negative history of syphilis and a consist-

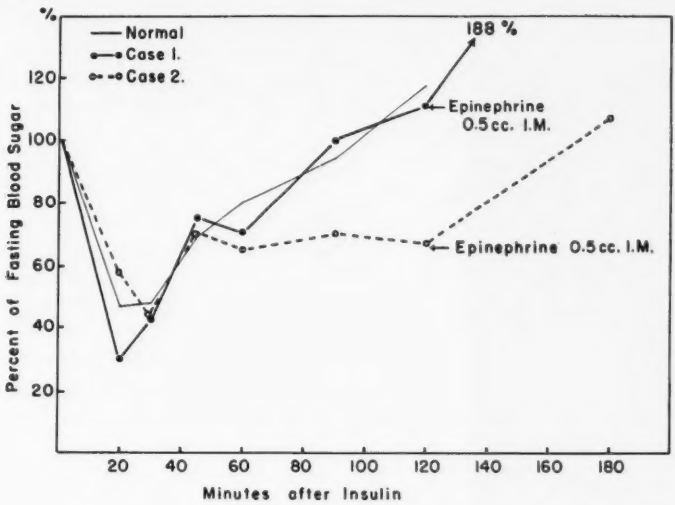

FIG. 3. The insulin tolerance test of both patients, as compared to the normal. Both tests differ from the normal, but are only partly consistent with hypopituitary disease.

unconscious for an unknown period of time. After recovery—the exact time could not be obtained—he developed "attacks" about once a month, during which he became semistuporous, lost his speech and had twitchings of his right hand. In the course of time, the face and right leg became involved. These attacks lasted a few minutes at a time. In 1925 he had a major convulsive seizure involving the right side. Also about this time he became pale and ceased to take interest in things.

In 1926 erections and libido failed and did not return until endocrine therapy was instituted many years later. From about this time on loss of axillary and pubic hair was noted. In 1928 he was treated at the Massachusetts General Hospital for six weeks for central ently negative spinal fluid Wassermann test and Gold Sol. Indeed he received antisyphilitic treatment over a period of two years. He was seen briefly in 1937, at which time he had a positive Hinton test and negative Wassermann test on the blood and a negative spinal fluid except for a protein value of 83 mg. per 100 cc. The severe pains,

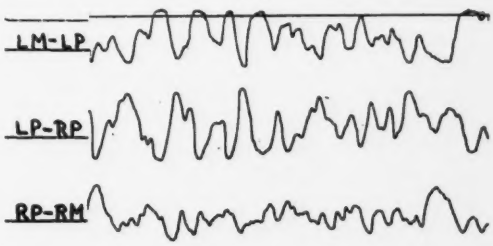

FIG. 4. The electroencephalogram in *Case 1*, showing three of the six leads. The letterings indicate the regions between which the potentials were measured: LM = left mastoid, LP = left parietal, RP = right parietal, RM = right mastoid.

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FIG. 2. a) A P view of the skull of *Case 1* showing the size and position of the bullet fragments; b) Lateral view of same. Note the location of the metallic particles, which extend from the floor of the fossa to the edge of the orbit.

which occurred in his legs and finally forced him to the hospital, were ascribed to tabetic crises, and note was made of Argyll-Robertson pupils.

In 1939 a diagnosis of myxedema was suggested and again in 1942, myxedema, secondary to hypopituitarism, was mentioned.

FIG. 5. Photograph of *Case 2* (C. H.) during treatment at the hospital.

As a result of these suggestions, he was referred to the hospital for study.

He complained of being inactive and sluggish, and of loss of appetite. He denied excessive thirst or urination, craving for salt, chilliness, sweating or faintness. He seemed vague about his symptoms and therefore unreliable. At the time of admission he had been married for 25 years without his wife's having become pregnant.

On examination, he appeared depressed and wept frequently. He was tall (176 cm.), weighed 70 kg., was well preserved but uniformly pale (fig. 5). His skin was smooth and free from pigmentation; axillary and pubic hair was absent; his beard was sparse, requiring shaving every other day. Both pupils reacted to light and the fundi were normal. There was fissuring at the corners of the mouth, red tongue and atrophy of buccal mucosa—a picture consistent with vitamin deficiency, but, according to Dr. Weisberger, also consistent with hypogonadism. The heart was normal in size, there was a soft systolic murmur over the precordium and the blood pressure was 125/80. The penis was small, the testes were small and soft and the prostate could not be felt. Neurological findings were entirely normal.

The important laboratory findings were as follows: the urine was normal; the erythrocyte count was 5.2 million; hemoglobin, 12–13 grams per cent; leucocyte count, six thousand; differential count and smear, normal except for hypochromia. The fasting blood sugar fluctuated between 55 mg. and 91 mg. per 100 cc., the blood sodium and chloride were normal, the blood cholesterol 156 mg. per cent, Hinton test positive, Wassermann test negative, and the basal metabolism ranged in the neighborhood of minus 30. The excretion of the 17-ketosteroids in the urine was 1.4 mg. per 24 hours and of FSH was less than three mouse units per 24 hours —both low values; testicular biopsy showed absence of Leydig cells and atrophy of the tubules with aspermatocytogenesis. The insulin tolerance test in this case also was partly normal and partly consistent with the condition. As indicated in figure 3, the blood sugar fell slowly after insulin to 43 per cent of the fasting value, but failed to rise very much after two hours. Roentgen ray plates of the skull showed a small sella, the visual fields were normal and the electrocardiogram showed bundle-branch block. The electroencephalogram, as indicated in figure 6, was grossly abnormal. There was a slow, beta rhythm, having an irregular, high-voltage activity. There were lateralizing features

which called attention to the right temporal and possibly the right occipital regions, and little disturbance occurred with overbreathing.

The diagnosis was obviously hypopituitarism with hypogonad and hypothyroid manifestations the most impressive, although other anterior pituitary functions were also deficient. In all probability, the head injury sustained in the War was the cause of his endocrine disturbance as well as of the convulsions.

In the treatment of this patient, the aim was to determine the effects produced by gonadotropic hormone, with and without thyroid. The results of this treatment will be reported elsewhere. There was marked improvement in endocrine status but no beneficial effect on the seizures.

It is interesting that at the time of the initial appraisal of this case, we wrote as follows: "As we have seen this condition in men it presents certain striking differences from that in women. The latter have a more progressive type and are far more easily thrown into adrenocortical insufficiency." This generalization seemed to hold in this case at first, but a few days after discharge from the hospital in January, 1944, he returned in acute adreno cortical failure initiated by an upper respiratory infection. He was brought out of coma in 12 hours by cortin and saline intravenously, and rapidly returned to his normal state. However, from this point on he began to go down hill. Adrenocortical failure persisted, with low levels of sodium and chloride in the blood, in spite of added salt and injections of cortical extract. He developed progressive anemia, slight fever, persistent joint pains—particularly in the knees—marked peripheral edema, repeated attacks of pulmonary edema and a diastolic rumble at the apex, which was inconstant. Some observers attributed the attacks of pulmonary edema to mitral stenosis; others attributed them to coronary heart disease with left ventricular failure, and considered the murmur to be due to left ventricular dilation. He finally died on April 13, 1944, in adrenal and congestive failure.

Autopsy showed a shallow pituitary fossa and a small fibrotic pituitary, which measured about 3×5×5 mm. (fig. 7). There was marked reduction in the elements of the posterior lobe as well as of the anterior lobe. The thyroid was small, weighing 9 grams, and histologically showed fibrosis, extensive lymphocytic infiltration and a small amount of colloid (fig. 8). The parathyroids were normal. The adrenals were small, together weighing 10.5 grams, and the cortical zone was

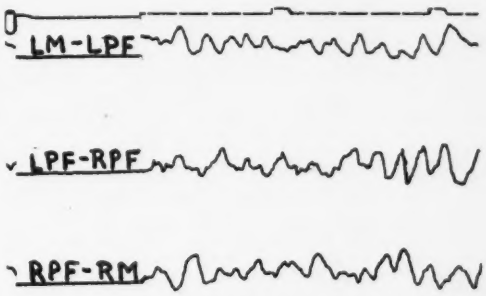

FIG. 6. The electroencephalogram in *Case 2*, showing three of the six leads. The letterings indicate the regions between which the potentials were measured: LM = left mastoid, LPF = left post-frontal, RPF = right post-frontal, RM = right mastoid.

moderately narrow (fig. 9). The testes were small and soft, each measuring 2×1.5×1 centimeters and a microscopic structure the same as the biopsy (fig. 10). The prostate was small and fibrotic, with glands which were few in number and simple in structure (fig. 11). The most surprising finding was rheumatic heart disease, old and recent. Undoubtedly the latter was the major factor in producing cardiac as well as adrenal failure.

DISCUSSION

It is common for epilepsy to result from head injuries, but it is rare for pituitary disease of the sort described above to follow such traumata. The various types of injuries—skull fractures, concussion, or penetrating foreign body—sufficient to destroy the pituitary usually cause death. In the literature one finds several reports of cranial trauma which caused symptoms suggestive of the adiposogenital syndrome, with or without diabetes

insipidus (Madelung, 2; Frank, 3; Marañon and Pintos, 4; Schaltenbrand, 5; Greene, 6; Gambigliani-Zoccoli and Boccuzzi, 7). Each of these authors, with the exception of Greene and of Gambigliani-Zoccoli and Boccuzzi, reported an example of this syndrome resulting from a bullet wound of the skull. However, none of the patients with this syndrome presented sufficient clinical evidence of Simmonds' disease.

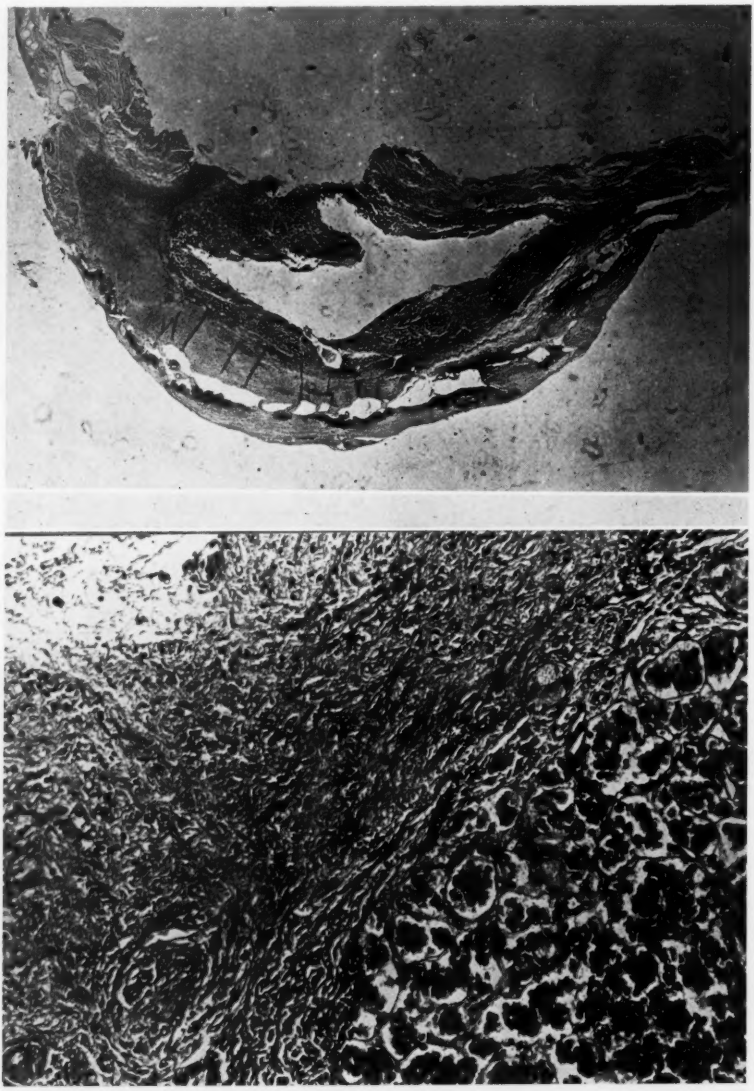

FIG. 7. Low-power view of the pituitary gland from *Case 2* at its widest point is shown on top. It is about a third of normal size. The higher power at bottom shows a portion of both the anterior and posterior lobes.

The case reported by Cyran (8) of a man who developed atrophy of the thyroid and loss of axillary and pubic hair following fracture of the base of the skull, and the several

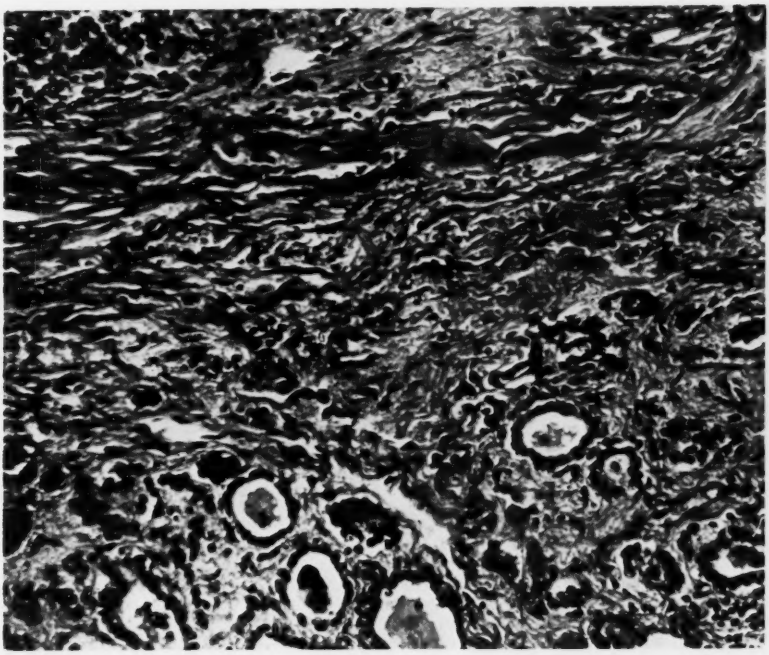

FIG. 8. The thyroid from *Case 2*, showing extensive fibrosis, lymphocytic infiltration and a few follicles.

examples reported by Stier (9) of loss of libido and of erections after head injury may be examples of the adiposo-genital condition. They hardly fall into the category of Simmonds' disease.

Only a few examples of pituitary cachexia due to cranial trauma are to be found in the literature. Reverchon and Worms (10) cited the case of a man, aged 34 years, who lost ten kilograms during the two months following a

FIG. 9. Low-power view of one of the adrenal glands from *Case 2*. The histology is normal but the gland is small and the cortical zone is narrow.

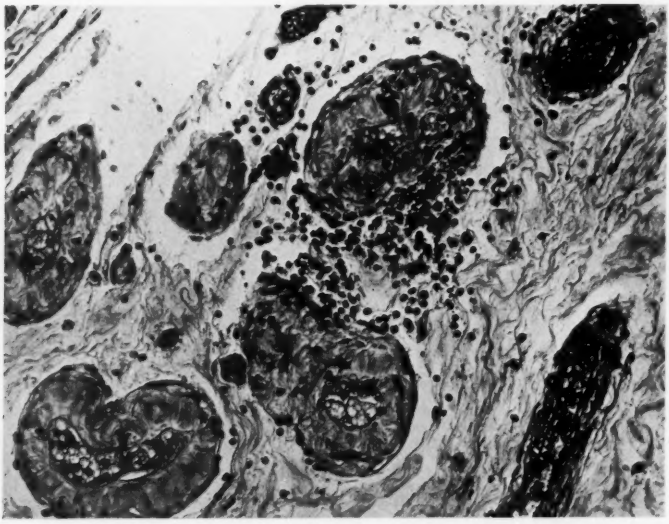

FIG. 10. Photograph of a section of the testicle from *Case 2*. The tubules are shrunken and widely separated by loose connective tissue, and are lined by irregular layers of undifferentiated cells. There are a few spermatogonia but no mitotic activity. No Leydig cells are seen.

fracture of the base of the skull. He also became weak, apathetic, anemic and finally died during an attack of syncope. Reinhardt (11) stated that hypophysial cachexia may follow fracture of the base of the skull if the sella is involved and that sudden death may follow. He mentioned one such case. Another case reported by Schereschewsky (12) was

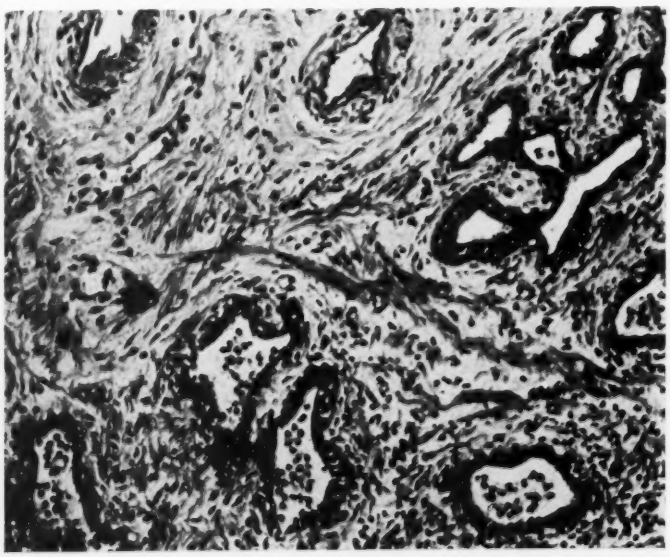

FIG. 11. Section of the prostate from *Case 2*. Note the extensive fibrosis and the paucity of gland structures.

complicated by diabetes insipidus. At autopsy the brain showed numerous small hemorrhages in the floor of the third ventricle and around the lateral ventricles. The pituitary was markedly diminished in size and the cellular elements were atrophied. The intermediate lobe was completely obliterated but the posterior lobe was normal. More recently, Escamilla and Lisser (13) reported two cases of Simmonds' disease following head injury. One of their patients developed the picture of pituitary cachexia after a fracture of the skull which resulted in an aneurysm of the right internal carotid artery with right exophthalmos. He improved after ligation of the carotid aneurysm.

The mechanism of pituitary or hypothalamic injury in the first of our cases is obvious, but not so in the second. It is likely that the force of the explosion produced hemorrhage in and around the pituitary or hypothalamus, thus causing damage to these structures. The finding of thick, adherent dura at the base of the skull is consistent with such an explanation.

It is conceivable that spontaneous convulsions in hypopituitary patients could be explained by hypoglycemia, which is more or less present in such individuals. That this is not the explanation is attested by the fact that other patients who were more "insulin-sensitive" or "hypoglycemia-unresponsive" than the two reported, did not develop convulsions, and that the electroencephalograms were not influenced by the blood sugar level. Moreover, these two patients are the only ones in a large series of cases of Simmonds' disease who had convulsions and a history of head injury. In *Case 1* there is still a third possible explanation for convulsions, namely, lead encephalopathy produced by the slow absorption of that metal from the bullet fragments. However, we believe that this explanation is not valid because there was no other evidence of lead poisoning and the excretion of lead in the urine was normal.

The electroencephalograms have proved to be of value in understanding the disturbances in the brain which cause convulsions. However, it is to be noted that in both instances the lateralization shown in the electroencephalograms was the opposite to that expected on clinical grounds. In *Case 1*, the evidence obtained from the electroencephalogram pointed to irritation on the left side, but the bullet fragments were to the right of the midline. In *Case 2*, the record called attention to the right-temporal and right-occipital regions, whereas the convulsions frequently involved the right side of the body. We have no explanation for this discrepancy.

As indicated above, our experience has been that men with hypopituitary disease are not as sick as women with this disease. They excrete more of the 17-ketosteroids in the urine than women do and they are not thrown into adreno cortical failure as easily as women. They may respond rather poorly to thyroid medication, but we have never encountered a male who developed adrenocortical failure from the ingestion of thyroid, just as we have seen it in the case of females. However, the course of events in *Case 2* indicated that the male is not entirely immune to the serious consequences of hypopituitarism.

The cause of death in this case was most unexpected. With a history of rheumatic fever late in life and the absence of any distinct murmurs, there seemed to be no reason to suspect rheumatic heart disease. Later, when joint pains, peripheral edema and a diastolic murmur at the apex appeared, this disease was suspected for the first time. In view of the autopsy findings, there is no doubt that the major portion of the clinical picture prior to death was due to rheumatic infection and to the adrenal failure initiated by this infection.

It is interesting to speculate on what rôle the injections of desoxycorticosterone acetate, cortin and saline played in the development of the acute rheumatic pancarditis. The demonstration by Selye *et al.* (14) of lesions characteristic of rheumatic fever produced in animals by injections of desoxycorticosterone acetate is pertinent. Moreover, according to Selye, certain conditions will increase the sensitivity of the animal to the noxious effects of desoxycorticosterone acetate. Among them are a high intake of salt, thyroidectomy and adrenalectomy. Since the patient with

hypopituitary disease lacks thyroid and adrenal function and is usually advised to take large amounts of salt, he is in just the right state to be affected adversely by desoxycorticosterone acetate.

However, our patient did not receive cortical extract until three months before death, when he came into the hospital in acute adrenocortical failure. At that time he received 50 cc. of cortin and 3000 cc. of normal saline solution in the first few days, and 4 grams of salt daily. In the two weeks' period before death, when evidence of rheumatic fever was already present, he received, in addition, 30 mg. of desoxycorticosterone acetate, 215 cc. of cortin, and 7000 cc. of normal-saline solution. It hardly seems likely that the small amount of cortical extract given three months before death could have produced the lesions of rheumatic fever found in this case. Moreover, the autopsy failed to reveal any evidence of nephrosclerosis or of periarteritis nodosa—two conditions frequently found in Selye's animals.

We have examined the autopsy material from two other patients who had received cortical extract and desoxycorticosterone acetate, in an attempt to extend Selye's experimental results to man. One was a patient with hypopituitary disease who had received moderate amounts of these materials two years before death and again ten days before death; the other was a patient with Addison's disease who had been given these substances a few weeks before death during a crisis and again the day before she died. Neither of these patients showed any histological changes suggestive of nephrosclerosis, periarteritis nodosa or rheumatic fever. An extensive study of such autopsy material will be necessary before any conclusions can be drawn regarding the rôle of the cortical hormone in the pathogenesis of these three diseases.

The problem of treatment of these patients will be the subject of another report. Suffice it to say that their gonads responded to stimulation by chorionic gonadotropin, producing clinical improvement as well as increase in excretion of 17-ketosteroids, and this in spite of the fact that these glands had been atrophied or 25–30 years. Thyroid in small doses was given in order to improve the myxedematous condition and extra salt was given to protect the patients against adrenal failure. In neither case were the epileptic seizures improved by the above therapeutic measures.

SUMMARY

Two patients with hypopituitarism and epilepsy are described. The first, a male of 46, was shot through the head at the age of 15. The bullet entered the left orbit, traversed the pituitary fossa and lodged behind the posterior clinoids. Growth and development ceased and gradually epileptiform seizures supervened. The second, a male of 48, was knocked unconscious by the explosion of a shell in World War I. He also developed epileptic seizures. They both presented characteristic clinical and laboratory evidence of hypopituitarism. They differed only with respect to stature. The first patient was a dwarf; the second, having received his injury at the age of 22, was of normal size. Their hypogonadal state responded to the administration of chorionic gonadotropin, but the convulsions remained unaltered. The second patient died after a siege of rheumatic infection which resulted in cardiac and adrenocortical failure.

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Treatment of Menstrual Disorders with Prolactin[1]

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New York City

PROLACTIN is one of the least frequently used fractions of the anterior lobe, in spite of the fact that it was the first active pituitary principle which, after isolation in absolute purity, has been brought to the point of crystallization. Its physiological properties are well explored; in addition to its effect upon the crop sac of pigeons and the mammary glands of mammals, prolactin is also important for body growth in general and to bring about the development of normal-sized viscera (15,19). Prolactin, furthermore, is antigonadotropic (15, 19), not only in birds but also in rats. Subsequent experiments with the purified hormone showed that, in addition to the inhibiting effect upon the secretion, release or effect of the pituitary follicle-stimulating hormone, prolactin also stimulates the luteal cells of the ovary, possibly increasing the secretion of the lutein body or at least, contributing to its maintenance (3).

Notwithstanding these experimentally demonstrable effects, the clinical use of prolactin in the past was almost exclusively limited to stimulation of the lactating mammary glands. Following the early reports of Kurzrok *et al.*, Ross, Kenny *et al.*, and others (13, 14, 20), even this therapeutic use practically fell into discard, partly due to disappointing observations and perhaps partly on account of strong local reactions which injection of the early, still impure preparations elicited. A revival of interest, however, is indicated by more recent publications according to which the lactogenic properties of the hormone can be used to good advantage (24).

The only other clinical use of prolactin was conceived by Hall (9) who successfully applied it for the treatment of functional uterine bleeding. Following his suggestions we tried to corroborate his clinical observations. Favorable results obtained in a group of seven patients were briefly mentioned in 1939 (5); further data obtained on a larger material were reported in subsequent publications (6, 7). In the course of these therapeutic investigations, the use of prolactin was extended to other related menstrual disorders and associated manifestations.

The experimental treatment of menstrual disorders with prolactin is based primarily on the data which indicate that prolactin antagonizes ovarian function, apparently by inhibiting secretion or release of the follicle-stimulating hormone of the pituitary. No matter what mechanism is involved, the decreased secretion of estrogen must affect the cyclic changes of the endometrium. It is justifiable to assume that under these circumstances proliferation of the endometrial glands will be inhibited or at least diminished, while concomitant changes of the stroma ought to include decreased vascularity and hence, a decreased tendency to bleed. If this hypothesis is correct, treatment of functional bleeding with prolactin aims in the same direction as radiotherapy or more recently, the use of androgens. The purpose of all these procedures is to suppress menstruation by decreasing or at least temporarily abolishing ovarian function up to a point which could be termed "functional castration." Following suppression of their function, the ovaries

[1] Most of the Prolactin used in these experiments was generously supplied by Dr. Frederick Fenger of the Armour Laboratories and Dr. Erwin Schwenk of the Schering Corporation.

gradually, or after a period of latency, resume activity; such claims for x-ray therapy were made by Kaplan (11, 12) while the widespread use of androgens proved its value by subsequent well regulated menstrual cycles in numerous cases. Prolactin therapy accomplishes similar results even up to the extent of complete amenorrhea which may last from one to several months. But even in those cases where the rhythm of the cycle is not interfered with, studies of the vaginal smear reveal changes indicative of suppression of estrogen secretion (9), comparable to those noted after administration of androgens or x-rays.

MENSTRUAL DISORDERS TREATED

The clinical material on which this report is based consists of 98 cases which are tabulated as follows:

Diagnosis	*Number of Cases*
Menorrhagia in Women of Childbearing age	30
Menorrhagia in Adolescent Girls	9
Menorrhagia in Preclimacteric Women (with or without uterine fibroid tumors)	10
Short Cycles (14 to 23 days) with or without Excessive or Prolonged Flow.	14
Midterm Bleeding	5
Dysmenorrhea with Menorrhagia	18
Acne Accompanying Dysmenorrhea and Menorrhagia	6
Premenstrual Bruising	6

MATERIALS AND METHODS

Prolactin treatment, although generally most satisfactory, has not given uniform results in all patients treated. The lack of uniformity may have been the result of individual differences in the reaction of the patients; some of the differences, however, were apparently referable to the preparations used. They came from different sources and although well standardized in respect to their lactogenic property, one could not escape the impression that their potency in respect to suppression of ovarian secretion varied from excellent to indifferent. The same patient occasionally responded promptly to one preparation whereas use of a different preparation gave surprisingly little effect.

The therapeutic procedure used as routine in menorrhagia was as follows:

The injections of prolactin were started with the onset of the menstruation; 200 units were injected intramuscularly every day until the bleeding subsided, but at least for four consecutive days. Thereafter injections were administered every other day for at least one additional week.

After two or three months of such treatment, consisting of repeated courses of seven to ten injections, a normal cycle was obtained in the majority of our patients. Thus, as a rule, the treatment could be terminated after three months; only a minority of the patients required subsequent attention.

The main complication which necessitated deviation from the routine procedure was a delay in the onset of the period following the first or second course of injections. Actual amenorrhea of several months' duration developed in a few patients. The incidence of amenorrhea after the administration of prolactin can be either ignored until menstruation sets in again spontaneously after one or several months, or if one feels more actively inclined, it is safe to follow Hall's suggestion (9) and use gonadotropins.

In those cases of amenorrhea in which gonadotropic therapy was decided upon, 250 units of chorionic gonadotropin was injected twice weekly with one cc. of an unfractionated anterior-lobe extract added as a synergist. Such treatment was started in patients who had reached the sixtieth day after their last bleeding without any signs of impending menstruation. In all cases so treated, menstrual flow set in within from three to five weeks of gonadotropic therapy.

The combined approach was used also in several cases in which the response to prolactin treatment alone was not satisfactory, i.e., the duration and/or amount of flow remained excessive. After two or three unsuccessful courses of prolactin injections, the next series of prolactin injection was followed up with injections of 250 units chorionic gonadotropin with the added anterior-lobe extract twice a week for the rest of the month. If the menstrual performance showed encouraging improvement, as it did in most cases, the combined treatment was repeated for a second month.

RESULTS

Menorrhagia in Women of Childbearing Age. The results in this group were truly excellent in the majority of cases. In 20 patients, normal periods were established both as to duration and amount of bleeding while considerable reduction of the flow and the length of bleeding was obtained in five patients. The effect of the treatment was not satisfactory in the remaining five patients.

The therapeutic response obtained has remained permanent in most of the patients. In a few cases, the flow became again prolonged and heavier, yet without approaching the pathological state preceding the treatment.

Menorrhagia in Adolescent Girls. The results in this group were not quite as good as in the mature women. Prolactin treatment was abandoned in one patient 16 years of age whose profuse bleeding could not be arrested even when the dosage was doubled. In three patients, prolactin treatment was combined with the use of gonadotropin. In one of these cases the combined treatment was used because of amenorrhea which lasted for two months, while in two patients the subsequent periods were delayed but still too heavy. Normal cycles and flow were established in all three after gonadotropic therapy was added for a period of three months. The other five patients in this group were treated with prolactin alone and responded with normal cycles and an altogether satisfactory flow.

Menorrhagia in Preclimacteric Women. Most of our failures occurred in this group, especially in the presence of uterine fibroid tumors. Entirely satisfactory results were obtained only in four patients who had no fibroid tumors, while fairly good results, i.e., decreased though still heavy flow, were obtained in two patients in spite of the presence of a fibroid tumor. In four other patients, three of whom had tumors, prolactin failed to bring about a significant decrease in either length or severity of the menstrual flow.

The results obtained in this group are definitely less good than those recorded by Hall (9) in a larger number of similar patients. Failure to curb consistently the menorrhagia of the preclimacteric woman does not particularly discredit prolactin for patients of this type are known to respond poorly also to other types of hormonal treatment such as the use of gonadotropins, progesterone or androgens.

Short Cycles. Most gratifying response was obtained in this group: we succeeded in lengthening the cycle in all patients so treated. A 28-day cycle, however, was not always obtained. In three patients with cycles of 14 days' duration and in five patients with cycles from 21 to 23 days, the treatment produced menstruations 27 to 28 days apart. The results were less good in the remaining six patients whose cycles, after termination of the treatment, varied between 23 and 26 days. The duration and amount of flow became satisfactory in all patients.

Minor relapses were observed in several instances, such as shortening of the interval to 24 or 25 days within a few months after termination of the treatment. Two patients of this type received a new course of prolactin therapy; in several other patients, the shortening of the cycle was successfully combated with gonadotropin given during the second half of two consecutive cycles.

Midterm Bleeding. Five patients were treated who had more or less copious bleeding at the time of ovulation. In all five, the midterm bleeding disappeared after the first course of injections and did not recur subsequently after the treatment was terminated. The number of patients in this group, however, is much too small to permit definite conclusions.

Dysmenorrhea. This group included patients whose abnormally heavy and prolonged menstrual flow was associated with severe and prolonged dysmenorrhea. General soreness of the abdomen preceded the flow for a period of up to 10 days; the actual menstrual pain in the form of severe cramps, subsided in most patients only several days after the onset of the profuse flow.

The results of treatment in this group were truly impressive: prolactin produced its effect within 24 hours and injections on two consecutive days were usually sufficient to control major discomfort. Even more striking

was the response to a single course of prolactin injections given during menstruation in respect to the following cycle, for the expected period of premenstrual tension and soreness either did not occur or was at least, considerably shortened and lessened. The menstrual pain itself was also either completely suppressed or greatly diminished. Continued prolactin treatment was similarly effective upon the menstrual pain of subsequent menstruations but even more remarkable was the persistent change in respect to the premenstrual period which the patients passed either with negligible discomfort or totally without prodromal symptoms.

The therapeutic results were permanent in most cases; recurrences were observed occasionally, yet their severity never approached that of the pretreatment level.

Two failures were observed in this group. Both patients presented the characteristics of severely neurotic personalities and remained unimproved in spite of all other hormonal or medicinal treatment.

Acne. The patients of this group differed from those of the previous group by manifestation of severe acneiform eruptions on the skin of the face and body. The results of prolactin therapy in respect to menorrhagia and dysmenorrhea were excellent in five and satisfactory in one patient. Gratifying improvement of the acne, however, was noticed in all patients: three appeared to be completely cured, for no recurrence was noted within a period of one to three years after termination of the treatment; in the other three patients, incidental outbreaks of minor severity occurred during subsequent menstrual periods. The result obtained is the more impressive because these patients previously had received the usual dermatological care with indifferent or at best, temporary results. Upon institution of prolactin therapy, however, all local treatment to the skin was discontinued in order to gauge the effect of the hormonal treatment.

Premenstrual Bruising. Of particular interest is the effect of prolactin in women who are prone to develop small, or even extensive hematomas during the premenstrual phase. While premenstrual bruising is a common phenomenon, it seems that those women bruise more readily whose menstrual flow is heavy or reaches the proportions of menorrhagia. The coincidence of increased bruising and abnormally heavy menstrual bleeding so far has not attracted the attention which it deserves, for it seems to suggest a systemic bleeding factor which affects the capillaries of the body in general and not only those of the endometrium.

Administration of prolactin during the first half of the cycle, as in the routine treatment of our menorrhagic patients, exerts but little influence upon bruising. If, however, prolactin injections are continued throughout the whole cycle or are given only during the second (postovulational) half of the month, the hemorrhagic tendency is suppressed or reduced to negligible proportions. We observed this favorable response in four patients. Two others responded with such violent local reaction at the site of injection that desensitization by intradermal injection of minimal doses seemed advisable. However, repeated attempts at desensitization were eventually abandoned, because they elicited considerable increase in the number, extent and painfulness of the subcutaneous hematomas.

DISCUSSION

The main advantage of prolactin therapy over other forms of hormonal treatment is its absolute harmlessness. Radiotherapy, though claimed to be applicable without undue danger in the adolescent (11, 12), is hardly the treatment of choice in women of childbearing age who may respond with permanent amenorrhea or sterility. Gonadotropic extracts, though their value has been questioned, may after prolonged use give satisfactory results. This treatment, however, is not immediately effective and is incapable of arresting profuse bleeding. Therefore it is of no value in combating menorrhagia, notwithstanding the fact that it may eventually regulate the menstrual flow if continued for an adequate length of time. Androgens are much more useful as a styptic and although the danger inherent in their use has been some-

what overemphasized, it remains unquestionable. Treatment with androgens must be carefully given and accurately timed. Androgenic therapy, moreover, is definitely ill-advised in patients with even mild hypertrichosis. A slight downy hairgrowth on the cheeks or upper lip, especially in women of dark complexion, should serve as a warning against the use of androgens. Acne, seborrhea or hair loss from the scalp are other weighty contraindications. The use of diethylstilbestrol in substantial dosage is not objectionable on similar grounds and constitutes an effective means of arresting excessive bleeding (10). Yet diethylstilbestrol is not tolerated by every patient and not infrequently causes nausea, vomiting, headaches, or dizziness. Nor is it unreasonable to object, as a general principle, to the unphysiologic high dosage of this powerful synthetic substance. Its use in the presence of fibroid uterine tumors would seem to be specifically contraindicated for it may accelerate the growth of such tumors.

Prolactin therapy is based on physiological principles; given in the estrogenic phase of the cycle, it is meant to curb the growth and vascular development of the endometrium. Whether or not the luteotrophic effect of prolactin is also operative, must be decided by further studies. Administration of prolactin prior to ovulation would hardly permit much scope for the luteotrophic effects. It remains to be seen whether or not the therapeutic results could be improved by continued administration of prolactin after the time of ovulation.

Our observations on premenstrual bruising suggest that a systemic bleeding factor is operative also in increasing bleeding from the endometrial capillaries. It would be conceivable that the styptic effects of prolactin are at least partly due to suppression of this hypothetical bleeding factor. The existence of such a factor and its probable origin in the spleen is supported by an increasing amount of evidence. Thus, it is well known that menorrhagia is a common symptom in purpura and splenectomy has been resorted to as a life-saving procedure (4, 17). Following splenectomy bleeding is almost immediately arrested, at a time when the blood platelet level is still very low, hence it is reasonable to assume that bleeding stopped when the bleeding factor supplied by the spleen was eliminated. These observations are fully in accord with earlier clinical experience in menorrhagia in which irradiation of the spleen proved to be just as effective as application of a full "castration" dose of x-rays to the ovaries (22). A connection between spleen and pituitary in the sense of a splenic-pituitary-ovarian functional interrelationship is suggested also by the findings that the anterior lobe of the pituitary enlarges after splenectomy (2) while removal of the spleen elicits an increased urinary excretion of gonadotropin (21). Enlargement of the spleen after injection of a crude gonadotropic extract was obtained by Perla (18); similar splenomegaly is observed also after castration (16), whereas the size of the spleen increases after parturition and remains small during lactation (1).

Experimental studies, previously presented by us as a preliminary report, also seemed to indicate that rats, injected with a pituitary extract reasonably free of prolactin, present enlargement of the spleen while injection of prolactin appears to elicit the opposite effect. Considerable differences in structure were also noted between the spleens of rats injected with prolactin or prolactin-free gonadotropic extracts, respectively (8).

SUMMARY

The treatment of functional uterine bleeding with prolactin is described and results of the treatment in 98 cases are reported.

Prolactin treatment shortens the duration and decreases the amount of the excessive menstrual flow.

The therapeutic response is less dependable in preclimacteric women than in women of childbearing age or in adolescent girls.

Short menstrual cycles can be adequately lengthened and midperiod (ovulation) bleeding can be prevented by well-timed injections of prolactin.

Dysmenorrhea, associated with menorrhagia, responds to prolactin therapy with disappearance or decrease in pain and pre-

menstrual discomfort. Premenstrual acne is also favorably influenced.

Premenstrual bruising can be diminished if prolactin is injected during the second half of the cycle.

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Studies on Pigmentation of Endocrine Origin[1]

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Pregnancy is normally associated with a deposition of pigment in characteristic areas already pigmented. Thus the nipples and areolae, the linea alba, the vulva, the navel and the face slowly accumulate pigment during gestation. The pigmentary response to pregnancy varies in different individuals. Brunettes show a greater response than do blondes. A Japanese, Nishizaki, suggested that the degree of pigmentation is an excellent index of the general physical response to the stimulation of pregnancy. In a few individuals, the increased pigmentation of the face involving the cheeks, the forehead, and the bridge of the nose presents a characteristic picture which has been designated as the "mask of pregnancy," or chloasma gravidarum. These areas of increased pigmentation gradually lose their excessive pigment and slowly fade out after the patient's delivery.

In recent years the pigmentary response of pregnancy has been regarded as endocrinal in origin. The first experimental evidence for melanin formation in the mammalian skin by hormonal action was presented by Lipschütz in 1930. This author transplanted ovaries into kidneys of castrated male guinea pigs and observed considerable pigmentation around the nipples after the operation. Similar results were obtained by Bloch and Schrafl in castrated male guinea pigs after the injection of estrogens. These experiments definitely involved the female gonad in the mechanism of pigmentation.

CLINICAL OBSERVATIONS

A group of young women with primary amenorrhea were treated with diethylstilbestrol after all other measures had failed. A diagnosis of primary ovarian failure was made in these young women, although admittedly it is difficult or impossible to differentiate between the amenorrhea which results from pituitary and that which results from ovarian failure. Characteristically, these girls were taller than average with the typical physique of the pre-adolescent. A delayed closure of epiphyses was commonly observed. Secondary sex characters were under-developed. The breasts were not prominent; the nipples and areolae were tiny and pink. Axillary and pubic hair was scanty. The external and internal genitalia retained their prepubertal characters.

After starting the oral administration of one milligram of diethylstilbestrol daily these young women matured rapidly and their reproductive organs reached a normal state of development. It was noted that in addition to marked growth, the nipples and areolae pigmented intensely (figs. 1 and 2). The linea alba resembled the linea nigra of pregnancy. In one instance, lightly pigmented moles became considerably darker in color (figs. 3 and 4). The characteristic mask of pregnancy did not develop although increased pigmentation

[1] This work has been done under a grant from the Douglas Smith Foundation of Medical Research for the University of Chicago.

[2] Was killed recently in service.

of other areas may have occurred. The intensity of the pigmentation reached its maximum three or four months after the institution of therapy at which time the nipples and areolae were almost black in a few patients. The degree of pigmentation far exceeded that seen during normal gestation. Continued medication resulted in a moderate regression of the color but the nipples and areaolae remain dark brown after four years of therapy.

The absence of hyperpigmentation in women during the menopause and postmenopausal period when treated by estrogenic substances is a striking observation in view of the above findings. We have observed some 1000 patients with menopausal complaints who have received estrogens for a year and longer since 1939. Ovarian failure associated with the menopause responds most satisfactorily to estrogenic therapy. These patients have received as much as a milligram of stilbestrol per day, the dosage gradually decreasing as the symptoms are brought under control. These patients did not exhibit an increase in pigmentation in the usual localities even though the total dosage of estrogens far exceeded the amount administered to the young girls with primary amenorrhea. One must conclude that the different behavior of these two groups of patients is indicative of some variation in the underlying endocrinal mechanism for pigmentation. Ovarian failure in young women with primary amenorrhea is different endocrinologically than ovarian failure associated with the menopause.

The function of the pituitary gland in the young women with primary ovarian failure is essentially normal. The pituitary gland, however, undergoes obvious change with the advent of the menopause. Sevringhaus examined the hypophyses of a number of old women and found an increase in the basophiles together with widespread vacuolization. A colloidal matrix displaced the cytoplasm in some of these cells, crowding the nucleus to one side and producing a "signet ring" appearance. Fluhman has reported an increased amount of follicle stimulating gonadotropin in the blood and urine of patients in the menopausal and post-menopausal period. The appearance of this gonadotropic material in the blood and urine is coincident with the development of the characteristic menopausal symptoms. It is possible that this follicle-stimulating gonadotropin may inhibit the pigmentation normally induced by estrogens.

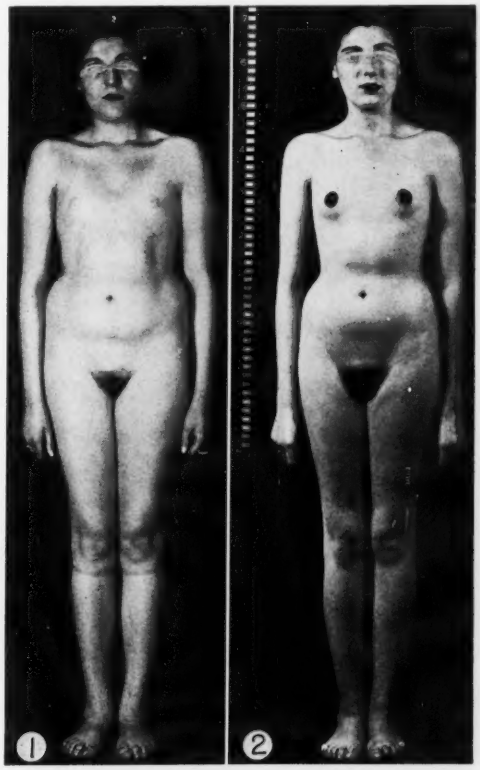

FIG. 1. *S.B. Unit No. 150466.* A young woman with primary amenorrhea before estrogen substitution therapy was started. Note the lack of development of the nipples and areolae and the absence of pigmentation.

FIG. 2. *S.B. Unit No. 150466.* This photograph was taken following the administration of 1 mg. of diethylstilbestrol for four months. Note the development of the breasts and the intense pigmentation of the nipples and areolae.

EXPERIMENTAL PRODUCTION OF HYPERPIGMENTATION

A series of animal experiments were planned to help elucidate the mechanism of estrogenic pigmentation. The castrated young male guinea pig was found to be the best

laboratory animal in which to study pigmentary responses. Young males weighing 125 to 275 grams were used in all of the following experiments. No particular color predominated in the animals used, although they were carefully selected so that at least one nipple was surrounded by dark hair. Bloch and Schrafl, Bloch and Guldberg, and others drugs such as diethylstilbestrol were as effective as the natural estrogens in the induction of pigmentation. Ten animals were injected every other day with 25 gammas of diethylstilbestrol dissolved in 0.1 cc. of sesame oil. A control group of ten guinea pigs received sesame oil subcutaneously in the same amounts. Five days after the institution of treatment

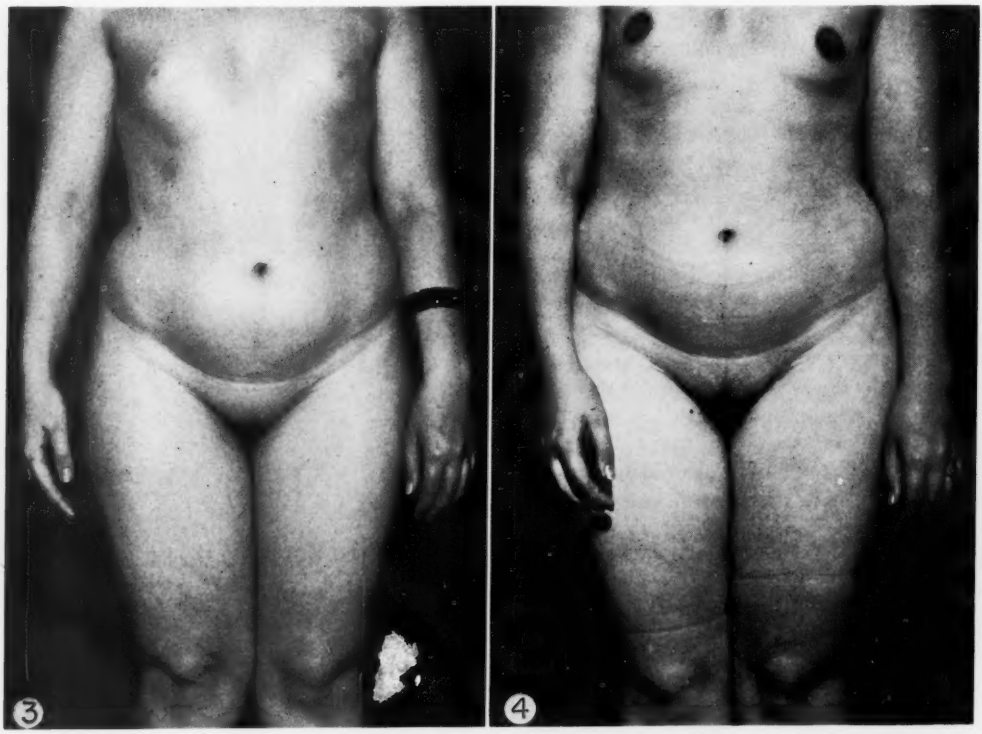

FIG. 3. *R.F. Unit No. 21949.* This photograph was taken before the onset of stilbestrol therapy. Note the lack of breast development and the absence of pigmentation of the nipples and areolae.

FIG. 4. *R.F. Unit No. 21949.* This photograph was taken following the daily administration of 1 mg. of diethylstilbestrol for four months. There has been a marked enlargement of the breasts, most striking in the nipples and areolae. Note the intense pigmentation of these structures, as well as the increased pigmentation of many small moles which were hardly evident prior to therapy. The increased pigmentation of linea abdominalis is likewise evident.

have noted that pigmentation could not be induced by estrogens in the areolae of albino nipples and in areolae surrounded by non-pigmented hair. The guinea pigs were castrated; they were ready for the various injections several days after their complete recovery from this operation.

The first experiment carried out was designed to show whether synthetic organic the guinea pigs receiving stilbestrol began to show considerable pigmentation about the nipple. The intensity of the pigmentation increased daily, reaching its maximum at the end of the second or the beginning of the third week. At this time the areolae were dark brown or black. The skin about the scrotum became increasingly more pigmented. The growth effect of the estrogens on the nipples

and areolae was likewise very evident. Continued injections over a period of two months did not alter the intensity of the color, once maximum pigmentation developed (figs. 5 and 6).

Others have noted that artificially pigmented areas induced by the natural estrogens show an increased activity of the dopa-oxidase, so the conclusion was drawn that the estrogenic hormone activates and increases the potential capacity of pigment formation in skin areas where such an inherent capacity had been present. Microscopic preparations made from sections of the areolae showed the basal layer of the epidermis densely filled with melanin granules. The "dopa" reaction carried out according to the modification of Becker *et al.* was extremely strong and many dendritic cells were seen to be filled with "dopa" melanin (fig. 7). The histologic picture of the pigmented areolae resembled the biopsies obtained from our young women in whom marked pigmentation of nipples and areolae developed following the use of stilbestrol (fig. 8).

The control group of guinea pigs which received oil alone showed no pigmentation macroscopically or microscopically during the first four weeks of treatment. In a few of the animals a faint darkening of the areolae was evident at the end of from eight to twelve weeks of injections, apparently as a result of the maturing of these animals (fig. 5). This insignificant change was not at all comparable to the pigmentation artificially induced during the first two weeks by estrogen administration.

Other estrogens were administered to groups of eight animals in an attempt to evaluate their effectiveness as pigment-inducing agents. The first group received subcutaneous injections of 50 gammas of estradiol benzoate in sesame oil every other day. To a second group of guinea pigs was administered 50 gammas of the synthetic organic estrogen, hexestrol, in sesame oil. A third group of eight animals were given a single injection each of 1000 gammas of methyl ether of stilbestrol in oil. A fourth group of animals were used as controls and received only sesame oil. All the estrogens induced marked pigmentation of the areolae resembling in

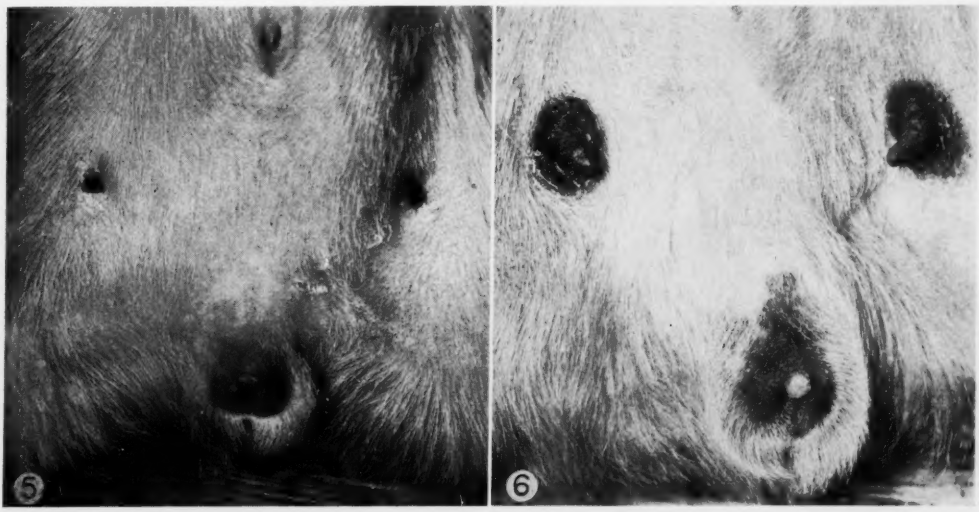

FIG. 5. Guinea pig used as a control; received twenty daily injections of 0.1 cc. of sesame oil. The nipples and areolae are small and show little pigmentation.

FIG. 6. Guinea pig which received daily intramuscular injections of 25 gammas of diethylstilbestrol in 0.1 cc. of sesame oil for twenty days. Note the intense pigmentation as well as the increased size of the nipples and areolae.

every way that produced by diethylstilbestrol. The intensity of the pigmentation reached its maximum at the end of two weeks and was as marked as in the group of animals which received diethylstilbestrol.

Methyl ether of stilbestrol is metabolized in the body and stilbestrol, the active estrogen, slowly liberated. It has been demonstrated clinically that a single subcutaneous administration of this estrogen will continue to be effective for several weeks. The guinea pigs receiving this estrogen rapidly developed pigmentation which continued to increase in intensity for three weeks. This was probably accomplished by the slow liberation of the stilbestrol.

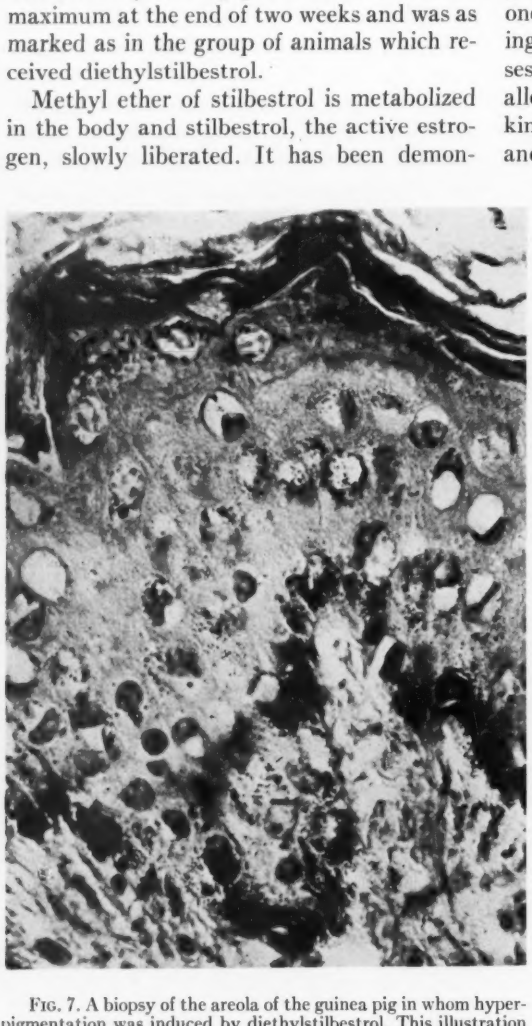

FIG. 7. A biopsy of the areola of the guinea pig in whom hyperpigmentation was induced by diethylstilbestrol. This illustration shows a strongly positive Dopa reaction with basal and dendritic melanoblasts filled with melanin granules. ×850.

The local effect of estrogens was explored in the following experiment. In eight castrated guinea pigs, stilbestrol was applied locally to one nipple. Three drops of a solution consisting of 0.1 milligram of stilbestrol in one cc. of sesame oil were dropped on one nipple and allowed to dry without manipulation of any kind. The other nipple was used as a control and simultaneously treated with three drops of sesame oil. After the second treatment an erythema of the areola of the stilbestrol-treated nipple developed. The nipple was more prominent and appeared congested. The opposite nipple had not changed. After ten such treatments, pigmentation of the areola began and this increased in intensity with the continuation of the medication. The control nipple developed no erythema, the areola remaining unchanged in color but increasing somewhat in size (fig. 9).

This experiment indicates that the action of estrogens on the melanoblast cells in mammals is a direct one without interference of general systemic effects. It has been reported that the action of testosterone propionate on melanin formation in the bill of sparrows is also a local effect.

The mode of the local action of estrogenic substances on melanoblasts is not understood as yet. Preliminary experiments in our laboratory seem to indicate that estrogenic substances have no effect on the oxidation of tyrosine to melanin *in vitro*. Especially, no effect was observed on the spontaneous oxidation of "dopa," if the slightly water-soluble alpha-estradiol was added to aqueous buffered solutions of dopa. Recent *in vitro* experiments seem to indicate that estrogens act by releasing the inhibitory action of glutione within the melanoblasts.

THE EFFECTS OF GONADOTROPINS ON EXPERIMENTAL HYPERPIGMENTATION

The second series of experiments were planned in an attempt to explain the clinical observations concerning the pigmentation of young women with primary ovarian failure

and the lack of pigmentation of the menopausal group of women.

A group of 10 castrated guinea pigs received every other day 25 gammas of diethylstilbestrol and 10 Cartland Nelson units of equine gonadotropin intramuscularly. A control group of 10 guinea pigs received 25 gammas of diethylstilbestrol in sesame oil. Pigmentation of the usual localities appeared in all of the animals at the end of four or five days, reaching its maximum intensity at the end of 12 to 14 days. The hyperpigmentation was of equal intensity in the animals of both groups.

Equine gonadotropin resembles in its action extracts of the anterior lobe of the pituitary. It contains follicle-stimulating as well as follicle-luteinizing properties. It will produce normal follicle growth, ovulation and corpus-luteum formation.

Two other groups of 12 animals each were used for the next experiment. The animals in the first groups received subcutaneously every other day 25 gammas of diethylstilbestrol and 75 I.U. or 0.1 cc. of chorionic gonadotropin.[2] The control group of 12 guinea pigs received only 25 gammas of stilbestrol in sesame oil. The simultaneous administration of stilbestrol and chorionic gonadotropin resulted in a striking inhibition of the estrogen-induced pigmentation. These animals showed no pigmentation of the nipples and areolae at the end of three weeks of injections. The nipples rapidly enlarged and outgrew in size the nipples of the animals receiving stilbestrol only (fig. 10). The growth of the duct system of the breasts was not inhibited. Pigmentation developed at the end of four or five days in the characteristic manner in all of the animals of the control group and the color reached its maximum intensity at the end of the usual two weeks.

[2] The preparation used was "APL", supplied by Ayerst, McKenna and Harrison.

On the continued administration of estrogens and chorionic gonadotropin some pigmentation occurred at the end of four to six weeks. However, this delayed response was faint indefinite, and very variable and in no way comparable to the characteristic response obtained by the use of estrogens alone in four or five days.

Chorionic gonadotropin is unlike mare-serum gonadotropin in that it contains little follicle-stimulating property but a considerable amount of the luteinizing factor. It is probably the result of chorionic cell activity for it appears in high concentration in the urine of women during normal pregnancy and in the presence of hydatidiform mole or chorionepithelioma. It does not inhibit the pigmentation of pregnancy. This apparent discrepancy between clinical observation and our experimental data in the guinea pig deserves continued observations. Pigmentation of pregnancy and artificially induced pigmentation by estrogens are both dependent

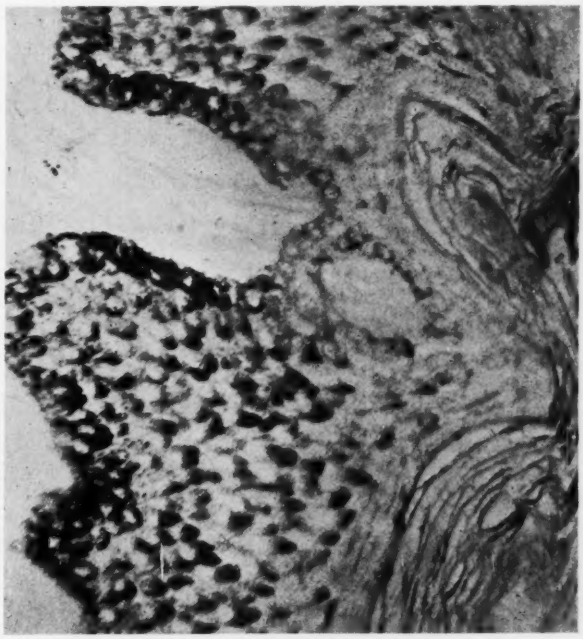

FIG. 8. A biopsy of the areola of the nipple of the young woman in fig. 2 after the development of hyperpigmentation by estrogens. The histologic appearance is comparable to that seen in fig. 7.

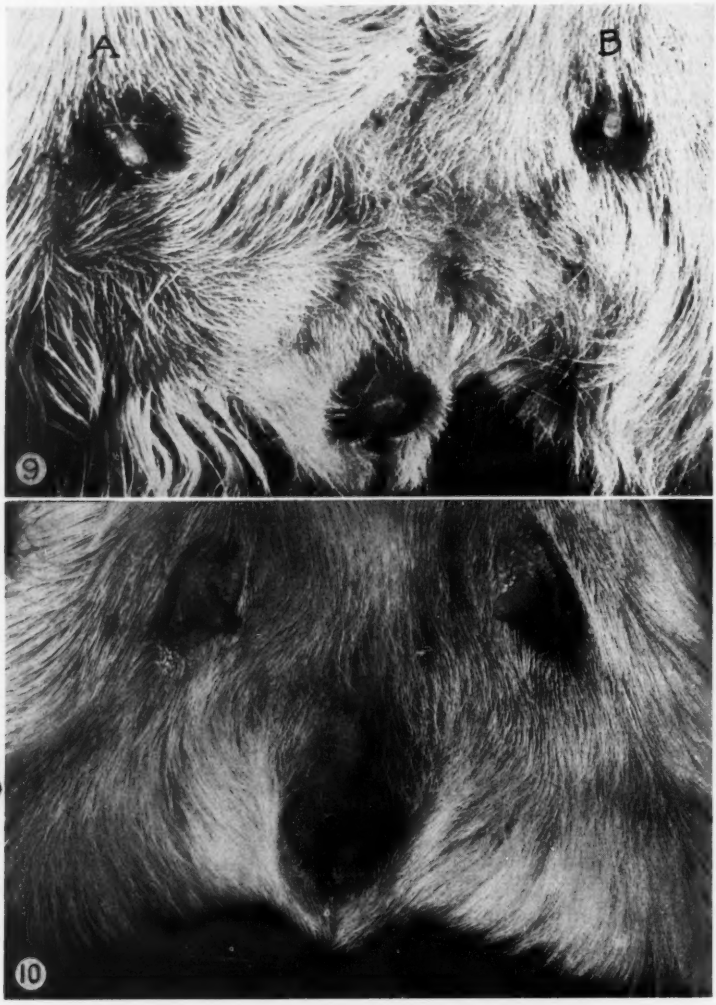

FIG. 9. Guinea pig in which nipple and areola (A) were treated by topical applications of diethylstilbestrol in sesame oil while nipple and areola (B) were used as a control and received topical applications of sesame oil only. The enlargement and hyperpigmentation of A demonstrates the direct action of estrogens on the melanoblast cells without interference of general systemic effects.

FIG. 10. Guinea pig which received a daily injection of 25 gammas of diethylstilbestrol in sesame oil and simultaneously 0.1 cc. (75 I.U.) of chorionic gonadotropin. Note the characteristic growth of the nipples and areolae but the striking absence of pigmentation. Thus, chorionic gonadotropin inhibited the hyperpigmentation induced by estrogens.

on a pituitary-gonadal relationship. In this relationship estrogens can replace the absent or ineffective gonad when the anterior lobe of the pituitary is functioning normally.

Prolactin is the fraction, obtained from the anterior lobe of the pituitary gland, that controls lactation in some animals. Lahr and Riddle have shown that in rats it is capable of interfering with ovarian activity thereby disrupting the estrous cycle. The effect of this anterior lobe fraction on the estrogenic pigmentary response was evaluated on a group of eight guinea pigs. These animals received 25 gammas of diethylstilbestrol in sesame oil

and 25 I.U. units of prolactin simultaneously every other day for a period of two months. To a control group of eight animals was administered 25 gammas of stilbestrol only. At the end of four days the animals in both groups began to show evidences of pigmentation in the usual localities. This pigmentation reached its maximum degree in the usual period of from 12 to 14 days. All the animals in both groups showed an intense pigmentary response. Thus, prolactin does not interfere with nor modify the pigmentation induced by estrogens.

The pigmentation in pregnancy suggested a possible rôle by the second ovarian hormone, progesterone. A group of eight guinea pigs received 25 gammas of diethylstilbestrol in oil and one milligram of progesterone subcutaneously every day for a period of six weeks. To a control group of eight animals was administered 25 gammas of stilbestrol alone. Pigmentation of the nipples and areolae of all the animals in both groups began at the end of the fourth day and became more intense until the maximum degree was reached within two weeks. Continued injections produced no further change. Progesterone did not inhibit the pigmentary response of the estrogenic hormone nor did it alter it in any way. We can assume that progesterone does not play a rôle in the pigmentation of pregnancy.

THE ADRENAL GLAND AND EXPERIMENTAL HYPERPIGMENTATION

The adrenal gland plays a vital rôle in pigmentation. The increased pigmentation seen in Addison's disease is well known. An attempt was made to rule out the adrenal glands as factors in estrogenic pigmentation. A group of 12 guinea pigs were castrated. Following their complete recovery a unilateral adrenalectomy was carried out according to the technic of Schachter and Beebe. At least one week intervened between this operation and the second adrenalectomy. The animals were kept alive by salt solution or desoxycorticosterone or a combination of both of these substances. In spite of these substitutes no animals survived the second adrenalectomy longer than eight days. However, in all the bilaterally adrenalectomized animals that survived longer than four days, the characteristic pigmentation of the nipples and areolae could be induced by the natural and synthetic estrogens and this pigmentation increased in intensity until their death due to adrenal failure. This experiment demonstrated that the adrenals do not exercise a rôle in the pigmentation produced by estrogens.

DISCUSSION

The physiologic pigmentation in the human female during pregnancy is the result of a normal pituitary gonadal relationship. The increased amounts of estrogenic substances present in the body during gestation predisposes to hyperpigmentation of the nipples, the areolae, the linea nigra, as well as to the characteristic deposition of pigment on the face with the production of the typical "mask of pregnancy." The pigmentary response varies in different individuals, but the hyperpigmentation is always limited to areas naturally containing pigment. The experiments recorded here confirm the rôle of the estrogens in physiological hyperpigmentation. Synthetic as well as natural estrogens provoke a characteristic response.

Primary ovarian failure is a diagnosis not easily established. Young women who fail to develop normal secondary sex characters, who do not menstruate, and who remain prepubertal in their physical development may have primary pituitary or primary ovarian failure. Estrogens administered as substitution therapy to these young women will produce physical and sexual maturity. Hyperpigmentation develops as a result of the establishment of a normal pituitary-gonadal relationship, by the substitution of estrogens for the absent ovarian function. It could be argued that a good pigmentary response in these young women is diagnostic of primary ovarian failure in the presence of a normal pituitary gland.

During the menopause, ovarian function decreases to a low ebb. Cyclic activity in the ovary slowly comes to a standstill. The anterior lobe of the pituitary is altered histo-

logically and functionally. The urine of the post-menopausal woman contains an increased amount of gonadotropins which are almost purely follicle-stimulating in character. The successful administration of estrogens for the relief of menopausal symptoms probably is to be accounted for by a neutralization or suppression of pituitary activity, but this therapy rarely results in the pigmentary response which follows its use in our young women with primary ovarian failure. It is possible that after the menopause the anatomical and the functional changes of the anterior lobe of the pituitary gland interfere with the development of hyperpigmentation.

A clue to this problem is present in our series of experiments designed to answer some of the questions raised in our clinical observations. Chorionic gonadotropin administered simultaneously with estrogens in our castrated guinea pigs inhibited the typical pigmentary response. Equine gonadotropin did not interfere with hyperpigmentation. The action of mare serum gonadotropin is like that of the anterior-pituitary lobe extracts. Chorionic gonadotropin will produce little change in the ovaries of most laboratory animals. Although it is present in large amounts during pregnancy in the human female, it does not interfere with the normal pituitary-ovarian relationship as regards the development of hyperpigmentation.

There are real differences between the pituitary ovarian relationships in primary ovarian failure, pregnancy and the post-menopausal period. These differences undoubtedly explain the normal pigmentation in pregnancy, the marked pigmentary response induced in young women on estrogen therapy, and the absence of hyperpigmentation when estrogens are administered during the menopause.

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Clinical Observations on a Case of Idiopathic Tetany and Epilepsy

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WE WISH to report a case in which epilepsy (grand mal) and idiopathic hypoparathyroidism with tetany occurred simultaneously. The patient was observed for a period of 2½ years. In this patient a correction of the hypocalcemia completely controlled both the tetanic manifestations and the epileptic seizures, despite the discontinuation of specific anti-epileptic therapy.

CASE REPORT

A white male, aged 23 years, gave a history of grand mal attacks which began at the age of 14. They were characterized by an aura of an "unusual" sensation in the mouth and extreme fatigue. followed by a typical cry, tonic convulsions, cyanosis, tongue-biting, foaming at the mouth, and unconsciousness that lasted 5–10 minutes, and was followed by sleep. Between 1933 and 1939 he experienced about 7 such attacks. In 1939 he became subject to spells of staring and swallowing two or three times a day. In addition the grand mal attacks became more frequent and occurred two to three times every month.

In 1939 he also noticed twitching and paresthesias in both arms and legs, and around the mouth. These spells were usually independent of both the grand and petit mal attacks, but sometimes twitching in the extremities preceded grand mal seizures.

From the family history it appeared that one maternal aunt had epileptic spells in childhood. Two cousins have had "nervous headaches."

His own previous medical history was uneventful except for a fractured toe and bruised hip following an automobile accident in 1940.

Physical examination revealed a well nourished, normally developed male of 23, height 67 in., weight 142 lbs.

The eyes reacted to light and accommodation. No fundal changes were apparent. Examination with the slit lamp revealed "moderately dense subcapsular, sheet-like opacities posteriorly, and anterior cortical dust-like golden opacities with peripheral globule-like precipitates. The diagnostic impression was: bilateral cataracta complicata."

The superior incisors show enamel defects consisting of horizontal ridging.

No abnormal findings were seen in the chest.

The pulse wate was 88 and the rhythm regular. The blood pressure was 120/80.

Neurological Findings

Sensation: normal
Movement, muscular power, tone, gait, speech: normal

Reflexes:		
	Corneal	+
	Pharyngeal	+
	Abdominal	+
	Knee Jerks	+
	Ankle Jerks	+
	Biceps, Triceps	+
	Babinsky	−
	Hoffmann	−

Laboratory Findings

Blood sugar, 75 mg. per cent
NPN, 37 mg. per cent
Wassermann, Kahn: negative
Urine, negative for sugar and albumin
Blood count, normal

Spinal Fluid

Clear fluid; cell count, 0
Pandy negative
Wassermann negative
Ross Jones negative
Sugar 62, Chloride 696 mg. per cent
Total protein 42 mg. per cent
Colloidal Gold curve: 34332211111.

Skull Plate

Conditions normal

Skiagrams of both Femurs

Markedly increased density of the bone structure.

[1] The department is in part supported by the Michael Reese Research Foundation.

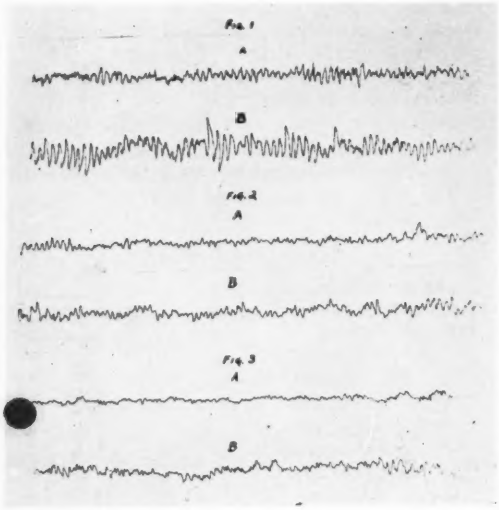
Electrocardiogram

"P-R interval 0.18 sec.; QRS inverted in lead 1 with an S1 present, upright in leads 2 and 3, and slurred in lead 1 and 3. T1 is tiny and diphasic; S-T 2 and 3 are depressened, T-4 diphasic and T-5 inverted. *Q-T prolonged.* Sinus rhythm, right ventricular preponderance, definitely abnormal curve." (Taken March 20, 1941.)

The values for calcium and phosphorus, and the clinical course as influenced by the treatment are summarized chronlogically in Table I.

Electroencephalogram[2]

Records were taken before and after hyperventilation. The first record was taken in March, 1941,



ELECTROENCEPHALOGRAMS OF PATIENT. (For description see text.)

while the patient was on phenobarbital therapy. His serum Ca at the time was 4.3 mg. per cent and the serum P, 8.4 mg. per cent (fig. 1 A, B). The second record (May 8, 1941) coincided with a serum-Ca level of 6.7 mg. per cent, and a serum-P concentration of 6.2 mg. per cent (fig. 2 A, B). The phenobarbital therapy had been supplemented with dihydrotachysterol and Ca lactate since April 23, 1941. The third record (June 3, 1941) was taken when the Ca and P levels had reached nearly normal values (Ca 9.5 mg. per cent) (fig. 3 A, B). Dr. Warren McCulloch of the Neurological Institute, University of Illinois College of Medicine, has interpreted these records as follows:

"All three show irregularities in rate and rhythm with some slow disturbances. In the first record there are frequent spiky wave forms which disappear progressively from the others, together with a decrease in amplitude. While all records are of the interseizure epileptic type the improvement is obvious. After hyperventilation the records are similar but the changes are more marked."

[2] The leads were placed on both parietal regions and on the vertex (100 MV).

DISCUSSION

The diagnosis of tetany was established in our case by the typical symptoms and signs characteristic of this disease: hyperirritability of the muscles, central cataract, characteristic teeth, low calcium and high inorganic phosphorus in the serum. The electrocardiogram showed the well-known prolongation of the S-T segment and other less characteristic changes of hypocalcemia. The bones showed increased density as described by Albright (1). As no history of injury to the parathyroid glands was given, we assumed that we were dealing with a so-called idiopathic tetany due to hypofunction of the parathyroid glands.

The diagnosis of idiopathic epilepsy was made on the basis of the typical grand mal seizures uniformly preceded by an aura. The electroencephalogram was compatible with the diagnosis. Spells of complete unconsciousness in tetany are rare and it is very questionable if they ever occur because of hypocalcemia. We are inclined to agree with Wilson (18) that all the cases in which seizures of complete unconsciousness are observed in tetany are epileptic in nature. Further electroencephalographic studies will have to prove this assumption.

The simultaneous occurrence of epilepsy and tetany was the subject of many speculations in the earlier literature. In recent years, since the pathogenesis of tetany has been more clearly understood and the mechanism of epilepsy considerably clarified by electroencephalographic studies, there is no doubt that the presence of both diseases is purely coincidental (Wilson, 18). Many clincial observations, however, reveal that both diseases may occur in the same individual. Such cases were encountered more frequently in Europe than in this country, because idiopathic tetany by itself has been seen more often in continental Europe than here. In 1911 Redlich (15) reported 11 cases and added 44 from other publications. Further observations were

TABLE I

Date	Treatment				Clinical Course	Laboratory Findings*	
	Phenobarbital	Calcium	Dihydrotachysterol	Viosterol		Serum Ca mg. %	Serum P mg. %
1941 March	gr. 1½ q.i.d.	—	—	—	Epilept. attacks twice monthly, petit mal several times a week. Tetan. attacks. Chvostek +++ Trousseau +++ (Wt.: 146 lbs.)	4.5 4.3	8.9 8.4
April 23	gr. 1 t.i.d.	Ca lactate 10 gm. daily	1 cc. daily	—	Has felt well, no seizures. Trousseau neg. Chvostek +	6.5	6.6
April 29	gr. 1 t.i.d.	Ca lactate 10 gm. daily	1 cc. daily	—	No attacks. Trousseau neg. Chvostek neg.	6.3	6.4
May 5	gr. 1 t.i.d.	Ca lactate 10 gm. daily	1 cc. daily	—	Same	6.7	6.2
May 20	gr. ½ t.i.d.	Ca Cl_2 10 gm. daily	1 cc. daily	—	Same	8.5	5.9
June 3	gr. ½ t.i.d.	$CaCl_2$ 10 gm. daily	1 cc. daily	—	Same	9.5	5.0
June 17	gr. ½ t.i.d.	$CaCl_2$ 10 gm. daily	1 cc. q. 2 day	—	Same	8.4	5.1
July 1	Discontinued	$CaCl_2$ 10 gm. daily	1 cc. daily	—	Same	10.0	4.7
July 29	—	$CaCl_2$ 10 gm. daily	0.5 cc. daily	—	Same	10.0	4.6
Sept. 20	—	$CaCl_2$ 10 gm. daily	discont. for 6 weeks	—	Same	8.9	5.4
Oct. 21	—	$CaCl_2$ 10 gm. daily	—	200,000 I.U. (4 cap.)	Same	10.0	5.0
1942 April 17	—	$CaCl_2$ 10 gm. daily	—	1 cap. t.i.d.	Same (Wt.: 148½ lbs.)	9.5	4.3
July 7	—	$CaCl_2$ 10 gm. daily	—	1 cap. t.i.d.	Same	10.2	3.9
Oct. 13	—	$CaCl_2$ 10 gm. daily	—	1 cap. t.i.d.	Same	9.8	4.0
1943 Feb. 9	—	$CaCl_2$ 10 gm. daily	—	1 cap. t.i.d.	Same (Wt.: 151 lbs.)	8.7	4.3
July 6	—	$CaCl_2$ 10 gm. daily	—	1 cap. t.i.d.	Same	9.7	3.9

* CO_2 combining power 69.8 Vol. %. Total proteins (plasma) 7.11%.

reported by Kalischer (9), Kotzle (11), Katzenelbogen (10), Falkiewicz (3), Findley (5), Roger (17), Guard and Kuntz (8), Geert-Jorgensen (6), Lindenbloom and Wientjes (13), Reiners (16), Beretervide (2), Fernbach and Szandanyi (4), and Lennox and Allen (12).

The relatively frequent combination of epilepsy and tetany, particularly in countries in which idiopathic tetany is more common, can

be more clearly understood since EEG studies have revealed that a large group of the population show the typical epilepsy pattern without exhibiting manifest seizures. Hypocalcemia is one of the factors precipitating epileptic seizures in persons who are potential epileptics (7). This is demonstrated by the course of our patient after successful antitetanic treatment.

When our patient was placed on dihydrotachysterol ("hytakerol") and calcium-lactate therapy, the blood calcium rose and the inorganic phosphorus fell to a certain extent. After substituting calcium chloride for calcium lactate, the blood values became quite normal. A similar observation of the fact that calcium chloride seems to be a better source of calcium than is calcium lactate was made by Albright (1). After seven months' treatment with dihydrotachysterol, viosterol[3] was substituted for it. The blood levels for calcium and phosphorus remained equally good and the patient started gaining weight. The interchangeability of the two drugs was recently discussed by McLean (14).

During the period from June, 1941 to the present time, the blood calcium and blood phosphorus remained normal, the Chvostek and Trousseau signs were negative, and the patient experienced neither tetanic nor epileptic attacks. The phenobarbital medication was decreased and finally stopped completely. Nevertheless, there was no recurrence of petit mal or grand mal attacks.

Although the electroencephalogram (fig. 1 C) is still abnormal even with normal blood-Ca and blood-P values, there has been a lessening of cortical excitability in comparison with the first record. This suggests that blood-Ca depletion may superimpose electrical changes upon an essentially mild interseizure pattern. Albright *et al.* (1a) in their report of several cases with Seabright-Bantam syndrome, mentioned epilepsy in one of them and briefly described the EEG changes from an epileptic pattern to normal in the course of antitetanic treatment. Recently Odoriz *et al.* (19) have described the types of EEG records in parathyroid insufficiency, their return to normal with therapy and their relation to epilepsy.

It is too early to draw conclusions from our observation on the relation of electrical discharges in the brain to calcium levels. It should be pointed out, however, that several studies in epileptics have revealed no clear-cut disturbances of calcium metabolism.

[3] The viosterol used was Ertron, kindly furnished by the Nutrition Research Laboratories, Chicago, Illinois.

SUMMARY

The case of a man, aged 23 years, suffering from idiopathic hypoparathyroidism and epilepsy is described. Therapy of the tetany (with Ca salts and dihydrotachysterol or viosterol) led to the complete cessation of the epileptic seizures despite a discontinuation of phenobarbital. It is probable that the low level of serum calcium acted as a trigger agent for the epileptic seizures.

We wish to thank Drs. S. Soskin and R. Levine for aid and advice in the preparation of this manuscript.

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The Clinical Evaluation of Insulin

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SINCE the discovery of insulin in 1921 by Banting and Best, numerous investigators throughout the world have attempted to modify the original product so as to improve its clinical action. Protamine zinc insulin was the first to achieve favorable recognition. Regrettably, the hopes of its early and enthusiastic proponents have been realized only in part. In the endeavor to procure one which will conform more closely to the physiochemical needs of the diabetic patient, a number of new combinations and preparations are being studied and reported. Several of the studies thus far published are not sufficiently well controlled to be trustworthy. There should be a clearer understanding of the fundamentals of the problems involved and an agreement as to adequate criteria before giving sanction to new products. In studies of this nature it is the practice of investigators to use known cases of diabetes confined to the wards of a hospital, also ambulant patients in the out-patient departments. The technique of study and its adequacy vary greatly. Some of the pitfalls and sources of error are here outlined.

It is exceedingly difficult to carry on an accurate metabolic study of a diabetic outside of a well-organized clinic in which the patient is housed, fed, and in which all factors are under strict control. The difficulties in the way of carrying on investigations on ambulant office patients or out-patients are so great that the data obtained must be regarded merely as trends or impressions. Furthermore, it should be recognized that a diabetic patient differs essentially from a depancreatized dog, both in the character and quantity of symptoms and physiochemical responses. The diabetic patient, with rare exceptions, whether on unrestricted or excessive diets, progressively breaks down at varying degrees of acceleration. Restriction of diet stays or retards this retrogression. Insulin of any kind or dosage does the same with varying degrees of improvement. A diabetic on a previously restricted diet will present a different reaction than will the one who has not been restricted. These facts must be recognized in the interpretation of experimental results. The only cases suitable for the comparative study of one therapeutic procedure with another are stabilized cases of long standing and fairly fixed diet and insulin responses. Such cases are not often available for extensive investigations. The criteria of evaluations and comparison are important.

Diabetes is a disease of impaired metabolism. Pancreatic diabetes is the type in which it is assumed that there is either a deficiency of insulin production or inhibition of its use in the liver. Other types of diabetes may be due solely to interference in insulin function rather than production. Pituitary disease, inflammatory gall-bladder, liver, pancreatic suprarenal and thyroid disease, and brain tumors are examples. These types are not suitable for comparative insulin studies. Glucose metabolism may be measured clinically by comparative studies of food ingested, with urine-sugar outgo and body weight. In making such studies the test patient should be on a balanced diet, from 30 to 40 per cent above basal requirement. Extremes in diet should be avoided. In such a study the individual under test should be on a diet adequate for his needs, yielding sufficient glucose to overtax slightly his capacity to store or burn. If it greatly exceeds his requirements, he will either convert the excess into fat with increase in body weight, or he will eliminate

it as urinary sugar or both. Furthermore, excessive ingestion of carbohydrate may materially affect insulin production and utilization and lead to false conclusions as to insulin requirements under normal diets. Under constant conditions the difference between the total glucose yield of the diet and the mean sugar outgo over a period of days or weeks will be the measure of utilization or glucose metabolism—assuming a constancy in body weight. The diabetic metabolizes glucose most efficiently when the blood sugar is within the normal range or slightly in excess of it. Abnormally low blood sugar after the ingestion of food and the administration of insulin means wasted insulin. Blood-sugar determinations to be of value should be made during periods of active digestion. They enable the observer to determine the efficiency of the technique, to regulate the distribution and spacing of both food and insulin injections and assist also in determining the size of individual doses. Fasting blood sugar determinations have only academic interest. In the early stages of acute diabetes or acute hepatitis they may serve to measure pancreatic or liver damage and recovery, but are valueless as a therapeutic guide when the injury becomes permanent. Glucose metabolism cannot be measured by blood-sugar observations. The same may be said of glucose-tolerance curves. Every clinician of experience frequently sees patients who on carefully controlled diets carry persistently high blood sugar levels, yet remain essentially urine-sugar-free. It is fatuous to attempt the evaluation of therapeutic procedures in diabetes by blood sugar tests alone. Furthermore, the oral glucose tolerance test, the method usually employed, is open to question. Lozner and his associates (1) and also Goldner and Haerem (2) have pointed out that defective absorption from the gastrointestinal tract, as well as disturbances of the liver, may vitiate the test. Lozner's group have substituted the intravenous-injection technique to avoid the errors of defective absorption. But there is still the more important question, do blood sugar curves measure glucose metabolism?

In the entire body of a seventy kilo normal individual the total amount of glucose is relatively small, ranging from 15 to 30 grams, while that which has been converted into glycogen and held in the various tissue reservoirs may total up to 1000 or more grams. These glycogen reservoirs are vital to the health of the individual. Their depletion produces a critical physiological state in diabetes and accounts for the readiness with which some patients go into coma, and the bizarre complex of reactions associated with glucosuria and elevated blood sugars. A practical clinical method for the estimation of glycogen reserves is a pressing necessity for an adequate interpretation of diabetes.

The common use of Benedict's qualitative solution as a quantitative method of measuring glucosuria and plotting the result in plus signs is to be deprecated. It is grossly inaccurate and misleading. Diabetics vary greatly in their output of urine—from 600 to 4000 cc. daily—depending largely on their fluid-drinking habits. Obviously, a small percentage of sugar in the urine in these extremes of output has a different significance. Benedict's qualitative solution is an extremely delicate test. A very small amount of sugar, under proper conditions, will rapidly reduce all the copper in the test as usually performed, and the resulting colors of the precipitate and solution depend quite as much on the technique employed as on the slight variations in the percentage of sugar; that is to say one-half per cent of sugar may produce a result indistinguishable from three per cent. When this error is combined with that which follows when the volume of urine is ignored, a one plus instead of representing a trace of sugar may in reality be a large amount. Conversely, a four plus might not mean more than one gram of sugar in the voided specimen. To attempt to estimate insulin requirements by such methods is fallacious, indeed. Only carefully collected twenty-four hour samples over a period of not less than one week should be used in total glucose-metabolism studies.

A comparative study of therapy in diabetes should extend over sufficiently long periods of time to exclude transient improvements or

relapses due to causes unrelated to treatment. Likewise, the study should be controlled by observation periods under like conditions both before and after the experiment. This is rarely done; usually the data from the casual and inexact therapy preceding a study are accepted as suitable criteria of the patient's metabolism. This, of course, is most unscientific and misleading.

The criteria by which we are to judge the merits of an insulin therapeutic procedure should be clearly set forth. For purposes of discussion the following are suggested. It is assumed that the patient under study presents a stabilized case of diabetes of long standing, free from any complicating disease which might interfere and sufficiently well-trained to be cooperative.

1. The patient should be on a 30 to 40 per cent maintenance diet which should be varied as little as possible during the test. This test diet should be instituted at least seven days before the actual experiment is begun. The weight of the food eaten at each meal should be actually determined and the total available glucose calculated. Even under the most stringent conditions the patient rarely eats exactly the prescribed diet. The variation may be as much as 40 per cent. It is a common error for clinicians to assume that the prescribed diet represents that which the patient eats.
2. In this preliminary seven days' period the patient should be given the standard insulin—preferably in three doses so that the maximum effect of the exogenous as well as the endogenous insulin may be exerted.
3. Total urine sugar for such twenty-four hour periods should be estimated.
4. Fasting body weight should be measured each morning.
5. Active-digestion blood sugar should be determined at least every other day and at any hour when there is suspicion of a reaction.
6. The patient should be required to take an amount of exercise, preferably walking, which would approximate light physical activity.
7. With these data from the seven days' control period as a base line, a two weeks' period substituting the test-insulin for the standard insulin should be begun, and similar data gathered.
8. This should be followed by a second control period like the first.
9. Careful watch should be kept for gastrointestinal disturbances in test patients. Faulty absorption of food for any reason is a potent cause of insulin reactions.
10. Many patients on insulin therapy of any kind, but particularly the slowly-absorbed varieties, may have reactions with scarcely appreciable symptoms. Reactions induce a factor of error of considerable importance into attempts to calculate the insulin requirement for a standard or test diet. For example, in the majority of patients, a blood sugar lowered to 75 mg. % or thereabouts, leads to suprarenal stimulation with the consequent release of glycogen from the various reservoirs of the body. It is not uncommon after a severe reaction to find in the urine as much as 30 to 40 gm. of sugar unaccounted for by the diet. A reaction means wasted insulin calling for either an adjustment in dosage or diet. Test-days in which reactions occur, therefore, should be excluded from final calculations.

If one wished to determine the efficiency of varieties of insulin with differing rates of absorption, this can best be done by studying output of four-hour periods with blood-sugar checks on the range in insulin activity. In such a test, due consideration should be given to the character and quantity of food that is ingested during these periods. Obviously, a meal composed of readily digested and absorbed foods will present a different physiological task to organs of metabolism than will a complex meal of slowly digested and slowly absorbed foods.

Finally, the clinical well-being of the patient is an important therapeutic index. Ex-

perienced diabetic patients are quick to notice changes in physical and mental vigor, and such expressions as "I feel better" or "I do not feel well" are voiced when a change in treatment-technique is made. Too much importance should not be attached to laboratory tests. Many patients may go for years with persistent glucosuria and high blood sugar and present no appreciable evidence of harm therefrom. Insulin confers a benefit on diabetic patients not measurable by laboratory tests. With it they live in fair comfort, regardless of the varying prevailing theories and practices. Without insulin they invariably retrogress and die.

For these and other reasons, the clinical evaluation of insulin or of therapeutic techniques is extremely difficult. Before new preparations of insulin are launched on the market, imposing great expense on manufacturers and new burdens on patients, clinicians and scientists who attempt to assay the value of a given product should set up a more definite and convincing set of standards of evaluation than now exists. If this is not done, in a short time the market may be flooded with insulin preparations of doubtful value for which the most extravagant claims may be expected, as was the case with drugs before the Banting era.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNA FORBES, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO MEMBRIVES, A. E. MEYER, DORIS PHELPS, E. C. REIFENSTEIN, JR., RUTH ST. JOHN, HAROLD WOOSTER, AND J. ZANARTU.

BOOK REVIEW

HOTCHKISS, ROBERT SHERMAN
Fertility in Men. J. B. Lippincott Company, Philadelphia, 1944.

SIEGLER, SAMUEL L.
Fertility in Women. J. B. Lippincott Company, Philadelphia, 1944.

A decade ago Meaker in his well-known book on human sterility called attention to the fact that many a wife has undergone laparotomy in the hope of attaining fertility when, as a matter of fact, the cause of the unfruitfulness of her marriage lay in lack of adequate sperm production by her husband. It has accordingly become a truism in well informed circles that the only judicious way to deal with childless marriages is first to determine the fertility of both partners. It is in cognizance of this principle that these two books by Hotchkiss and Siegler have been issued together in a single slip case. Both volumes are sponsored by the National Committee on Maternal Health.

"*Sterility in Men*" opens with a discussion of individual reasons why determinations of masculine fertility may be needed and with a delightful account of the psychological tactics that are often required to bring about the desired end. Succeeding chapters deal with genital anatomy, physiology and pathology; metabolism and composition of semen; methods of appraising fertility of men together with morphological features of the spermatozoa; influence of various factors on the semen; treatment of infertility; and commercial products. Field information on these various topics and their logical subdivisions is afforded in notably clear, concise and readable style. Excellently executed graphs and figures together with illustrative case histories aid in the elucidation of the text. Not the least of the virtues of the book is the human sympathy and understanding that are displayed. Thus a problem that might be superficially regarded as lending itself to almost mechanical treatment is shown to be what it is, namely one of psychological as well as somatic medicine. Well selected bibliographies open the literary gates for those who would journey further.

Siegler's companion volume on "*Fertility in Women*" is also admirably conceived and executed. It is generously illustrated with many graphs and photographs, some of the latter being in color. It likewise flows smoothly and is interesting and readable throughout.

"The book is written from a systemic or functional point of view and, wherever possible, structure, function and disease have been integrated to present a unified clinical picture." The scope of the book is largely determined by the very necessities of the case—a setting forth of the various causes of infertility together with diagnostic procedures for their detection and therapeutic means for their amelioration. The main topics treated are: the problem of fertility, methods of evaluation, history taking, the physical examination, female sex physiology, factors in infertility, and general and specific treatment. All the subtopics are included which a searching and scholarly treatment of the subject demands.

For those desiring to check the author's conclusion or to read further into the subject numerous well selected articles and books from the literature are cited.

Altogether, these two volumes bring the whole subject of infertility and its treatment up to date in authoritative fashion and accomplish admirably the purpose for which they were written.—*R.G.H.*

ADRENALS

KEMPER, C. F.

The treatment of Addison's disease by the implantation method. *Ann. Int. Med.* 22: 161. 1945.

Despite its limitations in correcting the metabolic defects in Addison's disease desoxycorticosterone is at present the agent of choice in replacement therapy, in the author's opinion. Administration by pellet implantation has the following advantages over injection of the hormone in oil: (1) decrease in cost by approximately 50% (2) constant delivery of hormone (3) obviation of the discomfort of daily injection. Desoxycorticosterone is marketed in sterile pellets weighing 125 mgm. It has been found that one of these pellets when implanted subcutaneously will give off approximately 0.5 mgm. of the hormone per 24 hours. To determine the requisite number of pellets for a given patient, the author recommends that the patient be given three grams of sodium chloride daily together with an initial dosage of 5 mgm. of desoxycorticosterone acetate (1 cc. of oily solution) by subcutaneous injection. Two or three months should be devoted to determining the patient's hormonal requirement as accurately as possible. When this has been done, sufficient pellets should be implanted to meet the patient's calculated need. The sodium chloride should be continued and its dose altered only when the symptoms so indicate. The patient's daily hormonal requirements should be re-determined and pellets re-implanted about once a year.—*J.M.*

SALGADO, C.

Virilization due to adrenal carcinoma. *Obst. y Ginec. Latino Am.* 1: 413. 1943.

A case report is presented of a typical adrenogenital syndrome in a 23 year old single female. The tumor weighing 600 gms. was found. The author found that the use of 1,000,000 international units of estrogen over a period of 60 days released the inhibitory effects of the tumor on the endometrium.—*J.Z.*

THORN, G. W., G. F. KOEPF AND M. CLINTON, JR.

Renal failure simulating andrenocortical insufficiency. *New Eng. J. Med.* 231: 77, July 20, 1944.

Two young adults without clinical evidence of previous renal impairment were admitted in a state of collapse with hemoconcentration, dehydration and hypochloremia. Since protein and formed elements were not present in the urine of either patient, both patients were treated initially with sodium, chloride and glucose solutions as well as adrenocortical hormone in an attempt to correct the apparent acute adrenocortical insufficiency. Dramatic improvement followed such therapy. Following restoration of plasma volume and blood pressure, however, azotemia persisted and kidney-function tests revealed marked and persistent high-grade renal insufficiency. Ultimately, it was shown conclusively that, whereas sodium, chloride and water were lifesaving, adrenocortical hormone preparations were of no value in the treatment of these patients. Sustained clinical improvement—for two and a half to four years—accompanied adequate sodium chloride and sodium bicarbonate therapy. Lastly, moderate hypertension, edema and moderate proteinuria developed terminally in both patients.

A new syndrome characterized by excessive loss of sodium, chloride and water, resulting in collapse and associated with renal disease rather than adrenal disease, is described. Adrenocortical hormone proved of no value in correcting the mineral depletion of these patients, since the renal tubular cell on which the hormone normally exerts its effect is unable to respond to additional hormone. Patients with chronic renal disease presenting evident signs and symptoms of sodium and chloride depletion may be said to be suffering from "salt losing nephritis."—*R.B.G.*

WARREN, F. L.

Estimation of urinary 17-ketosteroids in the diagnosis of adrenal cortical tumors. *Cancer Research* 5: 49. 1945.

Urinary excretion of 17-ketosteroids was measured in the urines of 19 male and 73 female patients. In 4 cases of adrenal cortical tumor in adult females extremely high excretions were found; in 2 of these cases dehydroisoandrosterone was isolated. Two cases of prepubertal virilism in girls also showed very high excretions, but isolation procedures showed the ex-

cess of androgen to be due to androsterone. A pregnant woman with virilism excreted large quantities of 17-ketosteroid; the child resulting from this pregnancy also showed an excessive excretion, but no explanation of these observations can yet be offered. About 10 times the normal excretion of 17-ketosteroids was observed in a patient suffering from carcinoma of the splenic flexure of the colon.—*Author's Summary.*

ARAYA, R.

Essential ideas in the ovarian histophysiology. *Obst. y Ginec. Latino Am.* 1: 293. 1943.

The ovaries of 50 women in various stages of the menstrual cycle were studied by serial section. The author observed: 1) absolute predominance of all forms of atretic follicles in comparison to the small number which reach ovulation; 2) atretic follicles undergoing an estrogen-progesterone phase and 3) thickening of the theca around the follicles and penetration of theca into the stroma. Sudan dyes demonstrated: 1) the presence of lipids in the primary follicles, in theca as well as granulosa cells, until fibrosis of the atretic follicles occurs; (2) lipid infiltration into the intracellular spaces of the cortical layer; and 3) accumulation of lipid-containing cells in the middle of the stroma.

The author believes that the presence of lipids in the stroma in all stages of development of atretic follicles establishes the continuity of ovarian hormonal excretion with the coöperation of several ovarian elements.—*J.Z.*

AYRE, J. E.

Cyclic ovarian changes in artificial vaginal mucosa. *Am. J. Obst. and Gynec.* 48: 690. 1944.

An 18 year old patient with congenital absence of the uterus, vagina and hymen had artificial vagina formed by the successive use of graduated wax molds. Vaginal smear studies were made following the completion of squamous epithelialization. The results revealed the new mucosa to be desquamating and reacting to ovarian hormones in a manner similar to the normal vaginal mucosa. The highest cornification level was 40 per cent. The authors believe this report makes it appear that cyclic phenomena occur in the vulvar squamous epithelium.—*E.C.H.*

DIONISI, H., AND P. SAMMARTINO

Conservative surgical treatment of the ovarian cystic tumors. *Obst. y Ginec. Latino Am.* 2: 89. 1944.

The authors make a plea for the enucleation of benign cystic tumors of the ovary with the preservation of as much parenchymatous tissue as possible. This is thought to be practical in all instances of either unilateral or bilateral involvement.—*J.Z.*

GORI, R. M., AND E. BAYONA

The vaginal contents of the newborn. The "Genital Crises." *Obst. y Ginec. Latino. Am.* 2: 532. 1944.

The changes in vaginal cytology of 200 newborn infants were studied. Full-term infants with and without vaginal crises and premature babies were included. The changes are more or less the same in all groups. Vaginal smears taken the first 3 to 4 days of life show a predominance of cells belonging to the upper layer whereas during the second week there is a gradual increase of elements proceeding from the deep layers of the mucosa.

Microscopic red blood cells are found in all infants not having a "Genital Crises." Therefore, this is only an accentuation of a normal process.—*J.Z.*

HERGER, C. C., AND SAUER, H. R.

Androgen control therapy in 130 cases of carcinoma of the prostate. *Surg., Gynec., & Obst.* 80: 128. 1945.

Orchidectomy alone, orchidectomy in combination with stilbestrol therapy and stilbestrol therapy alone were employed in the management of 130 cases of carcinoma of the prostate followed for periods ranging from 4 months to 2½ years. In 23 of the cases, external radiation to the pituitary was also given. The authors conclude that androgen control techniques afford the best method of palliation now available for inoperable and rapidly progressing carcinoma of the prostate. Although a considerable number of patients show a favorable initial response to treatment (disappearance of pain or decrease of pain, increase in weight or sense of well-being, improvement of obstructive symptoms, regression of the local lesion), there is an ever-increasing percentage of delayed failures

as time passes. The most favorable results were obtained in patients with metastatic lymph node involvement. All but one of these patients responded with complete regression of the metastases. Androgen control therapy did not prevent the development of bone lesions in patients with previously non-metastatic disease, nor did it arrest the spread of established metastases. The authors agree with Nesbit and Cummings that "the maximum benefit to the patient may be derived by delaying endocrine therapy until indicated by the onset of symptoms arising from advanced or metastatic lesions." They believe that castration should be reserved for patients with metastatic bone disease, patients in whom bony metastases are suspected or in whom rapid enlargement of the primary lesions becomes apparent. They regard castration as the most effective procedure if quick relief from pain is the object of therapy. In their experience orchidectomy preceded or followed by estrogen therapy offers no advantage over castration alone. Estrogen therapy alone they believe indicated in patients with operable carcinoma of the prostate who refuse surgery, in patients who refuse orchidectomy and in patients with moderately advanced lesions of low grade malignancy who have few or no symptoms. If changes indicating progression of the disease occur in these patients, castration should be done where possible. Relief of pain for varying periods was obtained in 10 of the 23 patients receiving supplementary therapy in the form of external radiation of the pituitary. —*J.M.*

INGRAHAM, C. B., W. C. BLACK AND E. K. RUTLEDGE

The relationship of granulosa-cell tumors of the ovary of endometrial carcinoma. *Am. J. Obst. and Gynec.* 48: 760. 1944.

The authors report two additional cases of granulosa cell tumor and one of theca cell tumor of the ovary associated with adrenocarcinoma of the corpus uteri. The rôle of estrogen elaboration in the production of carcinoma of the corpus is discussed. The question of definition of corpus cancer is reviewed.—*E.C.H.*

JOHNSON, C. G.

Arrhenoblastoma of the ovary. *Am. J. Obst. and Gynec.* 48: 724. 1944.

A proven instance of arrhenoblastoma of the ovary in a 24 year old colored female is reported with a nine month follow-up. The patient retained deepened voice and enlarged clitoris. She is still shaving, but less frequently. An atrophic progestational endometrium was found in the uterus at the time of operation. The other ovary contained a dermoid cyst which offers circumstantial evidence in support of the theory of teratomatous origin of ovarian arrhenoblastoma.—*E.C.H.*

MURRAY, E. G.

Gonadal stimulation with ascorbic acid. *Obst. y Ginec. Latino. Am.* 1: 437. 1943.

Eighteen patients with varying degrees of seminal inadequacy were treated with ascorbic acid. This was given parenterally, usually in doses of 0.50 grams every other day. The results indicate: an improvement in number of spermatozoa per cubic centimeter in 38 per cent; increase in motility in 81%; some increase in endurance; and in the 5 patients so studied, some improvement in morphology.—*J.Z.*

NOVAK, E.

Report of first 50 cases of the ovarian tumor registry conducted by the American Gynecological Society. *Am. J. Obst. and Gynec.* 48: 861. 1944.

Brief reports of these 50 patients are given. Among the tumors of endocrine interest are: granulosa cell carcinoma, 7 patients; thecoma, 4; arrhenoblastoma, 1; adrenal-cell tumor, 2; corpus luteum cyst, 1.—*E.C.H.*

RUBIN, I. C., J. NOVAK AND J. J. SQUIRE

Ovarian fibromas and theca-cell tumors: report of 78 cases of special reference to production of ascites and hydrothorax (Meigs' syndrome). *Am. J. Obst. and Gynec.* 48: 601. 1944.

The authors find that ascites is not a frequent occurrence in ovarian fibromas if one considers all fibromas including the small ones. Ascites alone and ascites plus hydrothorax are also found in association with theca-cell tumors. The authors believe the fluid probably originates from the tumor itself. Mechanism of and factors leading to hydrothorax are discussed.—*E.C.H.*

SALABER, J. A., A. E. NOGUES AND R. SAMMARTINO

Hyperplasia of the theca interna and hir-

sutism of a masculine type. *Obst. y Ginec. Latino. Am.* 2: 435. 1944.

A comparison is made between the ovarian tissue of 11 women with scant, infrequent uterine bleeding but without genital hypoplasia or hypertrichosis and 8 patients with infrequent, scant uterine bleeding, hypertrichosis and genital hypoplasia. All these patients received cuneiform resections of both ovaries. This procedure was associated with a return of cyclicity, occasional correction of sterility, but had no effect on the hirsutism.

In 6 of 8 patients in the latter group, hypertrophy, vacuolization and disintegration of the granulosa, as well as hyperplasia and vacuolization of the theca interna consecutively to the thickening of the limiting membrane and to the apparition of the large fusiform cells in the isolated focus in the middle of the stroma. The authors do not believe that it is possible to draw conclusions about the etiology or pathogenesis of the described alterations.—*J.Z.*

WALKINSON, J. M., G. E. GLORY, E. J. KING, AND A. HADDOW

Plasma acid phosphatase in carcinoma of the prostate and the effect of treatment with stilbestrol. *Brit. Med. J.* 2: 492. Oct. 14, 1944.

Acid phosphatase estimations were performed on the plasma of normal controls, of patients with conditions other than carcinoma of the prostate, and of cases of carcinoma of the prostate with and without metastases in bone. No case was treated by x-irradiation of the testes or by castration, and in order to obtain clear results in cases in which the prostate had been irradiated previously, time was allowed for the full effect of this procedure to be assessed before estrogen therapy was begun. Of ten cases of prostatic carcinoma, 6 showed a raised acid phosphatase content in the plasma; in 5 of these there was radiographic evidence of metastases in bone. Several of the results did not show any marked distinction between prostatic carcinoma with metastases and Paget's disease. The behavior of the plasma phosphatases, in cases of carcinoma of the prostate in which the plasma acid phosphatase was originally raised, was followed during treatment with stilbestrol. The response shows a uniformity of pattern, the acid phosphatase falling abruptly to a normal level, which is then maintained for considerable periods, with a rise in alkaline phosphatase followed by a gradual fall. Of 10 cases of carcinoma of the prostate 4 showed some degree of regression of the primary tumor under treatment with stilbestrol, and secondary deposits in lymph nodes underwent regression in 3 cases. X-ray examination at 3-monthly intervals in those cases with metastasis to bone revealed in some a progressive increase in density, while in others the deposits became more numerous during treatment or increased in size. With one exception all cases showed some measure of symptomatic and general improvement, in relief from pain, lessening of frequency of micturition, or gradual increase in hemoglobin level, and in improvement in appetite and gain in weight.—*R.B.G.*

ENDOCRINE GENERAL

DANOWSKI, T. S., AND A. W. WINKLER

Obesity as a clinical problem. *Am. J. Med. Sci.* 208: 622. 1945.

The authors have analyzed their experience at the Metabolism Clinic of the New Haven Hospital. A comparison is given of the complications occurring in 141 obese subjects with those in 100 control subjects. The composition of the population in these groups and the criteria upon which the diagnoses are based are stated. An unusually high incidence of varicose veins, of joint symptoms confined to the knees and ankles, and of hypertensive cardiovascular disease was found in the obese group, particularly in subjects less than 40 years of age. In obese patients with hypertension, the blood pressure fell in approximately one-half of the patients as the body weight was reduced. Hypertension usually did not appear in obese individuals as their weight increased further. In 67 of the patients the results of therapy aimed at weight reduction were analyzed. The plan of therapy consisted of: a) an ordinary diet altered sufficiently to produce a small negative caloric balance, and b) inculcation of correct eating habits over a long period of time. The calories varied from 1000 to 2000, with 1200 as the most frequent prescription. With this regime, successful weight reduction (loss of 30 pounds or more) was obtained in only a minority (12) of the cases. The authors conclude that reëducation in basic eating habits is essential for permanent reduction, and that the actual daily negative balance of calories is of much less importance.—*E.C.R., Jr.*

PARATHYROID

PERLMAN, R. M.

Parathyropituitary syndrome (pituitary dysfunction and "primary" hyperparathyroidism). *Arch. Path.* 38: 20. 1944.

A dog having atypical eosinophilic adenoma of the pituitary gland presented at autopsy coincident adenomatous hyperplasia of the parathyroid glands and grave chronic nephritis, together with fibrous osteopathy (von Recklinghausen) minus brown cysts. The case and experimental evidence support the concept of a parathyroid-pituitary relationship with consequent effect on the calcium metabolism.—*Author's Summary.*

WIGTON, R. S., AND F. BRINK, JR.

Studies of accommodation of nerve in parathyroid deficiency. *J. Clin. Investigation* 23: 898–903, Nov. 1944.

Nerve accommodation was tested in a normal subject and in 5 patients with parathyroid deficiency with and without treatment. The functional state of the peripheral nerves as measured by the property of accommodation was found to vary characteristically in these patients and the altered response curves to slowly increasing electrical stimuli could be quantitatively related to the blood serum calcium level. The authors suggest that the method may be used as a quantitative check on the clinical condition of patients suffering from hyperparathyroidism.—*T. H. McG.*

THYMUS

TORDA, CLARA, AND H. G. WOLFF

Effect of ether extract of the thymus and pancreas on synthesis of acetylcholine. *Proc. Soc. Exp. Biol. & Med.* 57: 69. 1944.

It has been reported that body fluids of patients having myasthenia gravis have the property of inhibiting synthesis of acetylcholine, a substance that is necessary for the transmission of nerve impulses. In some cases persons having myasthenia gravis have large thymus glands and experience clinical improvement following reduction of the thymus tissue. Therefore the influence of thymus extracts (as well as various control extracts) upon acetylcholin synthesis was determined. The anticipated inhibiting effect was demonstrated in extracts of thymus and pancreas but not in extracts of other control tissues. The serum of animals injected with thymus extract also had an inhibitory influence. The results would seem to support the thymogenic theory of the etiology of myasthenia gravis.—*R.G.H.*

THYROID

DEMPSEY, E. W.

Fluorescent and histochemical reactions in the rat thyroid gland at different states of physiological activity. *Endocrinol.* 34: 27. 1944.

The autofluorescence, birefringence, mineral salt distribution and oxidative enzymes of the rat thyroid were studied under conditions of different secretory activity. The phases of secretory activity were secured by exposure of the rats to hot and cold environments, by the administration of thyroxin or the antithyroid drug, thiouracil, or by combinations of these procedures. The intrafollicular colloid contained a substance which fluoresces blue, and which had solubility characteristics similar to those of thyroglobulin. This colloid component is directly related to the iodine content of the thyroid, since the iodine-poor colloid formed during administration of thyroxin and thiouracil lacked the characteristic blue fluorescence. It seems probable, therefore, that the fluorescence of the thyroid colloid is associated with the thyroglobulin content of the follicle. The connective tissue stroma and the thyroid follicular cells were also fluorescent. The fluorescent compounds of these elements were less soluble than was that of the colloid. Birefringent elements were observed in the follicular cells and in the stromal tissues. The connective tissue elements were increased in hyperplastic glands. Mineral salts were detected by the examination of microincinerated sections. The ash concentration within the follicular cells was decreased in hyperplastic glands. The possible relationship of this change to concomitant changes in fluorescence is discussed. Peroxidase and cytochrome oxidase were demonstrated in the thyroid follicular cells by the benzidine and the α-naphtholparaphenylenediamine reactions, respectively. The peroxidase reaction was easily inhibited by the addition of thiouracil to the reagents, while the cytochrome oxidase reaction was not affected by this treatment. These observations bear upon the mode of formation of thyroxin, and suggest a possible action of antithyroid drugs in preventing the synthesis of the thyroid hormone.—*Author's Summary.*

HUGHES, A. M.

Cretinism in rats induced by thiouracil. *Endocrinol.* 34: 69. 1944.

The continued administration of thiouracil to rats from the time of birth resulted in a marked retardation of growth, arrested development, mild anemia, and changes similar to those seen in cretinism. These effects, which are thought to be brought about by an inhibition of thyroid activity, were not observed if the injections were not made daily or if thyroxin was given concurrently. The young of thiouracil-treated mothers appeared to be normal but showed thyroid hyperplasia as early as 1 day of age and retarded development at 10 days, indicating the possibility of placental and mammary transmission of the drug. The functional activity of the thyroid gland appears to be essential to normal development as early as the 6th day of life.—*Author's Summary.*

KIBEL, I.

Hyperthyroidism and pregnancy. *Am. J. Obst. & Gynec.* 48: 553. 1944.

Of 12 patients with hyperthyroidism among 15,864 pregnant women, 8 went to term, 1 had operative interference in her thirtieth week of gestation, 1 aborted spontaneously and 2 had therapeutic abortions done on a cardiac basis. Subtotal bilateral thyroidectomy was done in 4 patients. The author believes that when possible, the pregnant women with hyperthyroidism should be carried to term, and only exceptional patients who fail to respond to medical treatment should be operated upon. The pregnancy should not be interfered with unless there is an obstetric reason.—*E.C.H.*

KINSELL, L. W., S. HERTZ, AND E. C. REIFENSTEIN, JR.

The effect of testosterone compounds upon the nitrogen balance and creatine excretion in patients with thyrotoxicosis. *J. Clin. Investigation*, 23: 880–90, Nov. 1944

Three thyrotoxic patients were observed on controlled diets while under treatment with testosterone propionate and methyl testosterone. A study was made of their general clinical condition; the basal metabolic rate; body weight; blood serum levels for phosphates, phosphorus, calcium, cholesterol, and potassium; and the urinary excretion of total nitrogen, creatine, creatinine, and 17-ketosteroids. Testosterone propionate was given daily in doses of from 25 to 100 mg., while methyl testosterone was always used in amounts of 100 mg. daily. Testosterone propionate routinely alleviated the symptoms of thyrotoxicosis; induced a markedly positive nitrogen balance; caused a gain in weight; brought about a retention of phosphorus, calcium and creatine; and effected a lowering of the levels of serum potassium. In contrast to testosterone propionate, methyl testosterone aggravated the symptoms of thyrotoxicosis, increased the basal metabolic rate, induced creatinuria, and was incapable of sustaining a positive nitrogen balance. In other respects its action was similar to that of testosterone propionate. The authors suggest that methyl testosterone may increase creatine formation at the expense of protein anabolism by drawing heavily upon stores of the essential amino acids, methionine and arginine. They conclude that methyl testosterone is contraindicated in the treatment of thyrotoxicosis, while testosterone propionate in daily doses of 12.5 mg. may prove to be a "useful therapeutic adjunct" in preparing thyrotoxic patients for operation, particularly those who have sustained marked weight loss with emaciation and muscle wasting.—*T. H. McG.*

SCHACHNER, H., A. L. FRANKLIN AND I. L. CHAIKOFF

On the *in vitro* accumulation of inorganic iodide by surviving thyroid tissue with radioactive iodine as indicator. *Endocrinol.* 34: 159. 1944.

Surviving thyroid slices were incubated at 38° in a bicarbonate-Ringer solution containing radioactive iodide as indicator. The amounts of I^{131} that entered the slices were compared with the amounts of I^{131} organically bound within the slices. Cyanide and sulfide, in addition to completely inhibiting the formation of thyroxine and diiodotyrosine, markedly depressed the accumulation of I^{131} by thyroid slices. Despite the almost complete inhibition of thyroxine and diiodotyrosine formation by 10^{-3} M azide, as much as 60 per cent of the Ringer's I^{131} entered the slices. Sulfanilamide, which strongly inhibited the *in vitro* conversion of Ringer's iodide to thyroxine and diiodotyrosine, had little effect on the iodine-concentrating capacity of thyroid tissue.

It is concluded that in thyroid tissue there

exists a mechanism for concentrating iodine that does not depend upon the conversion of inorganic iodide to thyroxine and diiodotyrosine.—*Author's Summary.*

SOSKIN, S., AND R. LEVINE

Recent advances in physiology of the thyroid and their clinical application. *Arch. Int. Med.* 74: 375. 1944.

This is a useful contribution to the physiology of the thyroid as it applies to the treatment of hyperthyroidism and should be read in its entirety to be fully appreciated. The remarks on the use of thiouracil are timely. "Shortly after the drug is administered the organism becomes unable to synthesize thyroid hormone at a normal rate, and the quantity of circulating hormone tends to fall. In response to this deficit an excess of thyrotropin is produced by the pituitary which stimulates the thyroid to hyperplasia and to the release of the normal thyroid hormone stored therein. Within 48 hours of the first administration of the drug these compensatory changes are histologically visible, and for a number of days this mechanism is adequate to maintain the metabolic rate at a normal level. Eventually, however, the store of normal thyroid hormone is exhausted, as evidenced by a complete loss of demonstrable colloid at the end of 7 to 10 days, and as new hormone can be made only at a reduced rate, the metabolic rate falls even though the thyroid hyperplasia is still advancing." It is too early to make any final general estimate of the value of treatment with thiouracil in hyperthyroidism. For one thing, it is not yet clear whether cessation of such treatment will result in a rekindling of the hyperthyroidism in some or in all instances. It may be that longer periods of treatment will not be followed by recurrence of the disease. There is the possibility that certain types of hyperthyroidism will yield permanent results while others will not. For example, hyperthyroidism which appears during a time of physiologic stress and strain, such as puberty, adolescence or the menopause, may very well be handled by tiding the patient over until the difficult period is past. For the time being the treatment should be regarded as an experimental procedure to be carried on cautiously and with constant supervision and observation of the patient. A careful watch should be kept for hitherto undetected toxic side reactions of the drugs. Thiouracil is preferable to thiourea or other derivatives. Even if no harmful side effects come to light we must guard against the dangers of overtreatment. Thiouracil given to the point at which a subnormal basal metabolic rate is obtained involves the possibility of 2 untoward results, both of them due to the reflex-stimulation of excessive secretion of thyrotropic hormone from the anterior lobe of the pituitary. This might cause an increase in the size of the goiter and initiation or exaggeration of exophthalmos. It is probable that both these dangers may be avoided by adding to the treatment the administration of $\frac{1}{2}$ to 1 grain (0.03 to 0.06 gm.) of desiccated thyroid per day. The administration of thyroid should not be started until the basal metabolic rate has been maintained at or about the normal level for 1 to 2 weeks. The facts which have been outlined represent a gratifying amount of progress within a brief period of time in a subject which had seemed almost dormant for many years. They should give particular satisfaction to the physiologist and the internist, who for so long have been faced with an essentially medical problem for which only surgery seemed to offer a practical solution.—*I.B.*